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## Title

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## A Perfect Storm: A Case of Thyrotoxicosis in the Setting of COVID-19 Infection and Methamphetamine Use

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#### **Case Presentation**

A 48-year-old male with past medical history of hyperthyroidism complicated by non-adherence with medication, methamphetamine dependence, and tobacco use disorder was brought into the Emergency Department by a friend for fever and weakness. He was found to be hyperthermic to 40.1C, hypoxic to 93% on room air, and tachycardic to the 190s. On exam, he was confused with proptosis and thyromegaly. His mental status subsequently deteriorated, and he was intubated for airway protection. Initial ECG showed atrial flutter with 2:1 block. Chest x-ray showed hilar infiltrates and subsequent PCR testing revealed the patient was COVID-19 positive. The patient was treated with potassium iodide (SSKI), propylthiouracil (PTU), beta blockade, steroids and cholestyramine. He was transferred to the MICU where initial thyroid testing showed undetectable thyroid stimulating hormone (TSH), elevated free T4 (FT4) at 4.48 ng/dL, and an elevated Free T3 (FT3) at 5.4 ng/dL. He was hyponatremic and hyperkalemic raising concern for adrenal insufficiency. Labs also revealed acidosis and an elevated creatinine. A bedside transthoracic echocardiogram (TTE) demonstrated reduced LVEF (30-35%) with global hypokinesis, neither of which were present on TTE in 2017. The patient was diuresised with furosemide. On hospital day 1, his liver enzymes became acutely elevated, with a more than 10-fold increase from admission (peak AST 773 U/L, ALT 567 U/L). PTU was stopped and methimazole was started. GI consultants felt the most likely explanation was shock liver secondary to transient hypotension after beta blocker initiation. On the evening of hospital day 2, the patient self-extubated and was weaned down to nasal cannula. He remained agitated and delirious. His heart rhythm spontaneously converted into sinus tachycardia and he was transitioned to oral medication and transferred to the floor where his liver function tests trended down, his renal function improved, and his hypoxia resolved. Steroids were tapered and total T3 and FT4 continued to decrease during course of the hospitalization. His mental status gradually improved, and he was discharged home of methimazole, carvedilol and hydrocortisone. Attempts to reach out to the patient for follow up and substance abuse counseling were unsuccessful.

### Case Discussion

Although the terms thyrotoxicosis and hyperthyroidism are often used interchangeably, thyrotoxicosis refers to a state of excess circulating thyroid hormone from any source while hyperthyroidism refers specifically to excess thyroid hormone released from the thyroid gland.<sup>1-3</sup> Thyroid storm is a rare but serious manifestation of thyrotoxicosis that impacts all organ systems.<sup>2</sup> Without prompt recognition and proper treatment, thyroid storm can be life threatening. Clinical presentations of thyroid storm can include fever, diaphoresis, agitation, anxiety, altered mental status, hepatic dysfunction, and cardiovascular effects such as tachycardia, arrhythmias, or congestive heart failure.<sup>4</sup> Typical laboratory results show elevated T3 and T4 levels and a low TSH. The Butch-Wartofsky scale was designed as a decision tool to aid in the diagnosis of thyroid storm, though the diagnosis remains clinical.

Thyroid storm is typically precipitated by an inciting event such as illness or abrupt discontinuation of anti-thyroid medication. This patient had multiple potential precipitants including his methamphetamines use and his infection with COVID-19. Methamphetamines are a commonly used stimulant whose effects on the central nervous system can mimic thyrotoxicosis through catecholamine surge. Methamphetamine use has also been shown to increase circulating TSH as well as free T4 which can further progress to thyroid storm.<sup>5</sup>

While Sars-CoV-2 is a novel virus responsible for the global pandemic, emerging literature and case reports show infection with this virus may be associated with a high risk of thyrotoxicosis. The pathophysiology has been described as a hyperactive immune response involving the Th1/Th17 lymphocytes, leading to downstream release of inflammatory cytokines, specifically interleukin 6.<sup>6</sup> The mechanism is thought to be the pro-inflammatory response from cytokine storm causing destructive thyroid gland.<sup>6</sup> Additionally, evidence suggests that the Sars-CoV-2 virus uses ACE2 and transmembrane protease serine 2 (TMPRSS2) expressed on the thyroid gland as a target molecule to enter, infect, and damage host cells.<sup>7</sup>

The mainstay of treatment of thyroid storm is to decrease the synthesis and release of thyroid hormones, block the effects of thyroid hormone on target tissues, and combat the resultant lifethreatening systemic decompensation.<sup>1</sup> Initial treatment includes beta-blockers to control the sympathetic hyperactivity of excess thyroid hormone decrease the conversion of T4 to T3. Antithyroid drugs or thionamides such as propylthiouracil (PTU) or methimazole are utilized. PTU may be preferred as it stops peripheral conversion of T4 to T3 in addition to inhibiting production of thyroid hormones. High dose steroids slow the conversion of T4 to T3 and empirically cover coexisting adrenal insufficiency. Adjunctive therapy with inorganic iodine blocks also thyroid hormone release. Cholestyramine is sometimes given to block enterohepatic reabsorption of thyroid hormone. Patients in thyroid storm also require aggressive supportive care which include cooling measures, blood pressure support, nutriation and airway management.1

In summary, the presence of concurrent COVID infection, and recent use of methamphetamine, both cofounded the diagnosis of thyroid storm, while also potentially precipitating onset. It is well known that intoxication with methamphetamine can increase heart rate, raise temperature and cause altered mental status. We describe a possible additional effect on TSH. At the same time, COVID-19 is an infection associated with an intense inflammatory state and cytokine activation, with additional potential for direct effects on the thyroid tissue. We postulate that the combined effects of these circumstances lead to sympathetic overflow leading to an unusually severe presentation of thyrotoxicosis.

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