


# Graves Disease Following the SARS-CoV-2 Vaccine: Case Series

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## Abstract

Widespread vaccination is a principal strategy to mitigate the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and lessen the global burden of coronavirus disease 2019 (COVID-19). Information is rapidly evolving about the impact of SARS-CoV-2 vaccines on the immune and endocrine systems. This case series heightens clinical awareness of possible thyroid effects and conveys knowledge of what to monitor, which are fundamental components of public health and pharmacovigilance. We present a case series of Graves disease following mRNA SARS-CoV-2 vaccination, with symptoms and altered thyroid function tests developing within 7 days of the first dose in 2 women aged 38 and 63 years, and 28 days after the second dose in a 30-year-old man. New-onset Graves disease occurred following administration of mRNA vaccines against SARS-CoV-2. Based on the timing of signs and symptoms relative to administration of the vaccine and the absence of other probable causes, we consider the vaccine as a potential contributor to the diagnosis. The viral spike protein, delivered indirectly through an encoded mRNA vaccine, may be capable of triggering an inflammatory cascade and immune response triggering thyroid dysfunction.

## Keywords

case report, COVID-19 vaccines, endocrinology, Graves disease, immunology, pharmacovigilance, SARS-CoV-2

## Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–producing coronavirus disease 2019 (COVID-19) pandemic is markedly affecting mortality and the global economy. As a principal countermeasure, rapid vaccine development using the mRNA platform and deployment in adults and adolescents is mitigating COVID-19 hospitalizations and deaths.

As knowledge accrues about the effect of newly developed vaccines on organ systems, we are learning that SARS-CoV-2 vaccines, like COVID-19 disease, may affect endocrine physiology, particularly thyroid physiology. In addition to the occurrence of Graves disease following COVID-19 infection,<sup>1</sup> this condition has recently been documented following SARS-CoV-2 vaccination.<sup>2–4</sup>

Here, we present a series of 3 adults presenting to a Cornell-affiliated hospital or endocrinology clinic in New York City between January and April of 2021 with new-onset thyroid dysfunction following SARS-CoV-2 vaccine administration (Table 1).

## Case 1

A 38-year-old woman received the SARS-CoV-2 vaccine (Pfizer-BioNTech, New York, New York) and 5 days later

presented to the emergency department with sudden onset left lower quadrant abdominal pain. Her presentation was consistent with thyroid storm given her fever, tachycardia to 140 beats per minute, and gastrointestinal symptoms (Burch-Wartofsky score 55).

Thyroid function tests revealed suppressed thyrotropin (TSH) of <0.008  $\mu$ IU/mL, elevated free thyroxine (fT4) of 108 pmol/L, and elevated total triiodothyronine (T3) of 10.3 nmol/L. Thyrotropin receptor antibody (TSHrAb), thyroid-stimulating immunoglobulin (TSI), and anti-thyroid peroxidase (TPO) levels were all elevated. Ultrasonography revealed a diffusely enlarged thyroid gland with heterogeneous echogenicity and increased vascularity consistent with Graves. She has no personal or family history of thyroid or

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**Table 1.** Demographic, Clinical, and Laboratory Parameters of Patients.

	1	2	3
Age (years)	38	63	30
Sex	Female	Female	Male
US vaccine <sup>a</sup>	Pfizer-BioNTech	Moderna	Pfizer-BioNTech
Days following vaccination (N) <sup>b</sup>	5 days after first dose	7 days after first dose	28 days after second dose
Clinical presentation	Tachycardia, fever, abdominal pain	Pruritic rash	Palpitations, tremor, weight loss, irritability
Initial TSH	<0.008 $\mu$ IU/mL	0.011 $\mu$ IU/mL	<0.005 $\mu$ IU/mL
Initial fT4	108 pmol/L	30.9 pmol/L	22.9 pmol/L
Initial T3/fT3	T3 10.3 nmol/L	T3 4.6 nmol/L	T3 2.5 nmol/L
TSI <sup>c</sup>	(+) >40 IU/L		(+) 0.95 IU/L
TSHrAb <sup>d</sup>	(+) 32 IU/L	(+) 22 IU/L	
TPO <sup>e</sup>	(+) 1730 IU/mL	(+) 1149 IU/mL	(-) 15 IU/mL
Reference intervals	TSH 0.45-4.5 $\mu$ IU/mL fT4 10.6-22.8 pmol/L T3 0.9-2.8 nmol/L TSI range < 0.5 IU/L TSHrAb range < 1.75 IU/L TPO range 0-9 IU/mL	TSH 0.55-4.78 $\mu$ IU/mL fT4 11.6-23.2 pmol/L T3 0.9-2.8 nmol/L TSHrAb range < 1.75 IU/L TPO range 0-9 IU/mL	TSH 0.45-4.5 $\mu$ IU/mL fT4 10.6-22.8 pmol/L T3 1.1-2.76 nmol/L TSI range <0.55 IU/L TPO range 0-34 IU/mL
Imaging	U/S: heterogeneous, hypervascular, enlarged gland	U/S: heterogeneous, hypervascular gland Scintigraphy: diffuse increased activity	None
Treatment	Methimazole, beta-blocker	None	Methimazole, beta-blocker

Abbreviations: TSH, thyrotropin; fT4, free thyroxine; TSI, thyroid stimulating immunoglobulin; TSHrAb, thyrotropin receptor antibody; TPO, thyroperoxidase.

<sup>a</sup>Vaccine administration under Food and Drug Administration Emergency Use Authorization.

<sup>b</sup>Time interval from vaccine dose to onset of thyroid-related symptoms.

<sup>c</sup>TSI: Case 1: Semi-quantitative chemiluminescent immunoassay, ARUP Laboratories; Case 3: Semi-quantitative immunoassay, Labcorp.

<sup>d</sup>TSHrAb: Case 1, 2: Quantitative electrochemiluminescent immunoassay, ARUP Laboratories.

<sup>e</sup>TPO: Case 1, 2: Quantitative chemiluminescent immunoassay, ARUP Laboratories, Case 3: Electrochemiluminescence immunoassay, Labcorp.

autoimmune disease. A computed tomography (CT) angiogram performed 1 year prior incidentally revealed thyroid gland enlargement measuring 7.3 cm in transverse diameter. She was treated with methimazole at a total daily dose of 60 mg titrated up to 80 mg along with propranolol 40 mg 3 times daily. After 2 months, fT4 decreased to 66 pmol/L, and after 3 months, it normalized to 23 pmol/L, while on methimazole, 80 mg daily in divided doses. After a discussion of the risks and benefit of administering the second vaccine, she decided to postpone the dose. She reported improved energy level and denied recurrence of palpitations or abdominal pain.

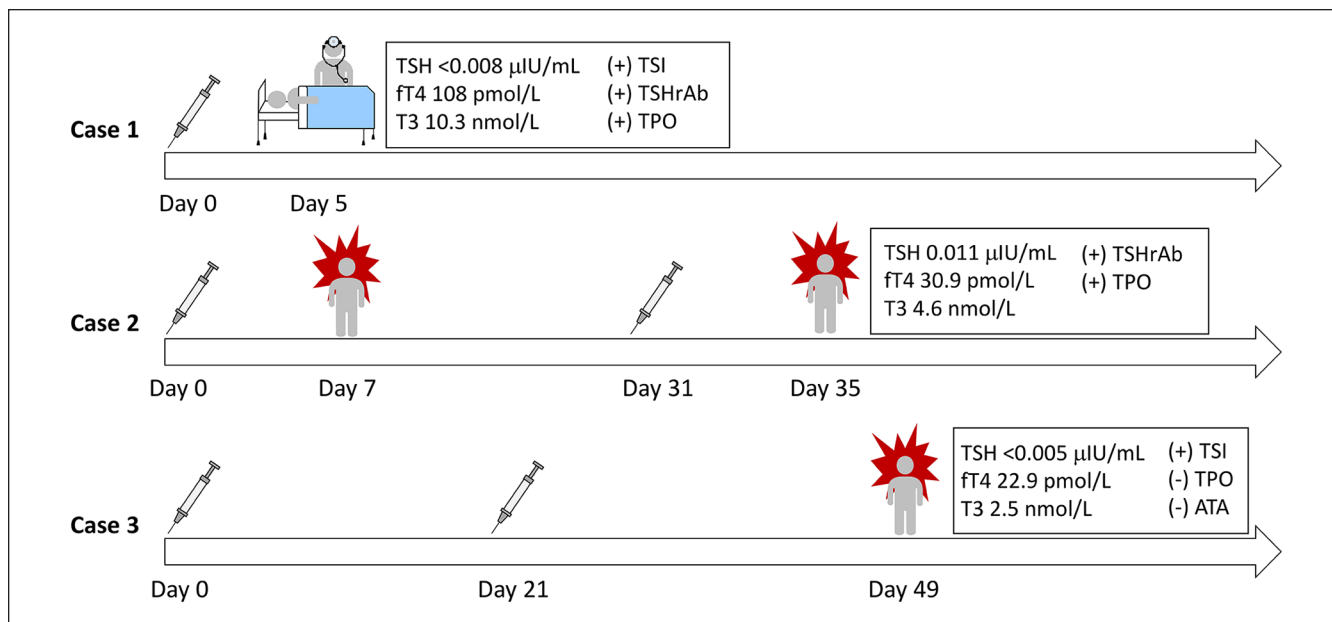
## Case 2

A 63-year-old woman received the first dose of the SARS-CoV-2 vaccine (Moderna, Cambridge, Massachusetts) and 1 week later developed a pruritic rash on her neck and upper chest. She had no palpitations, heat intolerance, distal tremor, or diarrhea. She received her second vaccine dose 31 days after the first dose. Four days after receiving the second vaccine dose, thyroid function tests were drawn, which revealed a suppressed TSH of 0.011  $\mu$ IU/mL and elevated fT4 of 30.9

pmol/L and T3 of 4.6 nmol/L. She had elevated TSHrAb, TSI, and TPO antibody levels. Thyroid ultrasound demonstrated a heterogeneous hypervascular gland along with 2 solid isoechoic nodules measuring 1.4 and 2.3 cm. She has no personal or family history of thyroid disease. Except for a sister and aunt with lupus, there is no other family history of autoimmune disease. She received no recent intravenous contrast. No antithyroid medication or beta-blocker was initiated as the patient was asymptomatic. After 6 months, the TSH remained suppressed at 0.01  $\mu$ IU/mL with a high-normal fT4 of 21 pmol/L. On thyroid scintigraphy, radio-tracer activity was high throughout both thyroid lobes with an elevated 24-hour uptake of 41%, consistent with Graves. The patient remained asymptomatic and no antithyroid medication was initiated.

## Case 3

A 30-year-old man received the second dose of the SARS-CoV-2 vaccine (Pfizer-BioNTech) and 4 weeks later developed irritability, palpitations, tremors, and restless sleep. These symptoms were accompanied by a 15-pound weight loss over 6 weeks. Thyroid function tests revealed a



**Figure 1.** Timeline depicts onset of symptoms in relation to severe acute respiratory syndrome coronavirus 2 mRNA vaccine administration in 3 patient cases. The initial thyroid function tests on presentation to their endocrinologist are shown, indicating thyroid abnormalities.

Abbreviations: TSH, thyrotropin; ft4, free thyroxine; TSI, thyroid stimulating immunoglobulin; TSHrAb, thyrotropin receptor antibody; TPO, thyroperoxidase; ATA, anti-thyroglobulin antibody.

suppressed TSH of <0.005  $\mu\text{IU/mL}$ , ft4 minimally elevated at 22.9 pmol/L, and T3 normal at 161 pmol/L. He had an elevated TSI and negative TPO and anti-thyroglobulin antibody (ATA). He has no history of thyroid disease and had a normal TSH level 3 years prior. His mother developed Graves disease postpartum. He has no personal or family history of autoimmune disease. Medication was initiated with methimazole 5 mg and atenolol 25 mg daily. Six weeks later, the TSH remained fully suppressed and ft4 was in the normal range at 14.9 pmol/L. His irritability and restless sleep improved; however, he still endorsed occasional palpitations.

## Discussion

In this case series, we present 3 patients who were vaccinated against SARS-CoV-2 and subsequently developed new-onset Graves disease. Patients ranged in age from 30 to 63 years and 2 were women. Two developed symptoms 5 and 7 days after the first dose of the vaccine and the third developed symptoms 28 days after the second dose (Figure 1).

Exploring thyroid pathophysiology associated with the SARS-CoV-2 vaccine involves considering how inflammatory processes are triggered by the virus, as a similar mechanism might be driving thyroid disease from the infection and the immunization. Thyroid abnormalities, including autoimmune thyroid disease, have been described following COVID-19.<sup>1,5</sup> After initial infection of the respiratory tract, the subsequent pro-inflammatory cascade of cytokine activation, that is, “cytokine storm,” may cause immune-mediated thyroid inflammation.<sup>6,7,8</sup> Could the pro-inflammatory state

and ensuing thyroid abnormalities observed in COVID-19 patients also occur in those receiving the SARS-CoV-2 vaccine? Three reports have been published of Graves disease after SARS-CoV-2 vaccination. Three days after receiving the Pfizer-BioNTech SARS-CoV-2 vaccine, 2 female health care workers exhibited symptoms of hyperthyroidism and were found to have thyrotoxicosis with imaging findings diagnostic of Graves disease.<sup>2</sup> Two further Graves disease cases were published, 1 patient diagnosed with new-onset Graves following his first dose of SARS-CoV-2 vaccine, and a second patient with recurrent Graves after vaccination following a 17-year period of remission.<sup>3</sup> Finally, a case of exacerbation of existing Graves disease is reported in a 30-year-old woman well controlled on low-dose methimazole who developed worsening hyperthyroid symptoms and thyrotoxicosis following 2 doses of the CoronaVac vaccine, further exacerbated by an additional booster.<sup>4</sup>

One mechanism by which a vaccine could trigger a deleterious inflammatory response is through an adjuvant in the formulation. While advantageous in developing an antigen-specific immune response, adjuvants can also trigger autoimmune disease such as Graves in genetically susceptible individuals.<sup>9,10</sup> While the novel SARS-CoV-2 mRNA vaccines do not include adjuvants, the mRNA is not only an immunogen but also could act as an adjuvant due to the RNA’s intrinsic immunostimulatory properties.<sup>11</sup> However, there is no definitive mechanistic explanation for autoimmune disease developing after vaccination and epidemiological studies to date do not support the hypothesis of adjuvant-induced autoimmune disease.<sup>12</sup>

There is limited experimental data concerning SARS-CoV-2 vaccine's ability to induce autoimmune thyroid disease. Investigators conducting an in vitro study to determine how strongly antibodies to the SARS-CoV-2 spike protein reacted with human tissues found that TPO demonstrated moderate cross-reactivity against spike protein antibodies. They further explained that TPO peptide sequences shared homology with several SARS-CoV-2 proteins, including the spike protein.<sup>13</sup>

Our case series corroborates recent case reports of Graves disease occurring after an SARS-CoV-2 mRNA vaccine. Based on the timing of signs and symptoms relative to administration of the vaccine and the absence of other probable causes, we consider the vaccine as a potential contributor to the diagnosis. However, a limitation is the onset of Graves could have occurred independently of the vaccine administration. Clinical awareness of possible effects and knowing what to monitor are necessary components of public health practice and pharmacovigilance. An epidemiological study of incident Graves disease among recently vaccinated and unvaccinated individuals in the general population could clarify the extent of the association between the SARS-CoV-2 vaccine and autoimmune hyperthyroidism. If this case series is further supported by epidemiological studies, it will be important to determine the underlying causal mechanism to optimize vaccine safety in the fight against the COVID-19 pandemic.

### Authors' Note

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### Ethics Approval

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

### Informed Consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

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