Aggravation of hyperthyroidism following severe acute respiratory syndrome coronavirus-2 mRNA vaccine booster administration in a patient with Graves' disease

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Introduction

The interrelationship between thyroid dysfunction and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccination was documented in several case reports during the COVID-19 pandemic. This article reports a case of aggravation of hyperthyroidism following the administration of SARS-CoV-2 mRNA vaccine booster in a 30-year-old

Case report

A 30-year-old woman with a history of Graves' hyperthyroidism, well controlled on carbimazole for more than 1 year, presented to endocrinology outpatients with palpitations, weight loss, and diarrhoea, a few days after receiving a Pfizer-BioNTech severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine booster.

She was initially diagnosed with Graves' hyperthyroidism in 2019, after developing symptoms of palpitations, hot flushes and unintentional weight loss for more than 1 month. Thyroid function tests at diagnosis revealed an undetectable thyroid-stimulating hormone level of <0.008 µIU/ml, and elevated levels of free thyroxine of 76.08 pmol/litre and free triiodothyronine of 30.8 pmol/litre. Thyroid-stimulating hormone-receptor antibody status was positive at a value of >40.00 IU/litre (reference range 0.1–1.0 IU/litre). Ultrasound of the neck showed diffuse enlargement of the thyroid gland without any definite nodule or cervical lymphadenopathy.

The patient was rendered euthyroid within a few months of carbimazole initiation. She had remained clinically and biochemically euthyroid on a minimum dose of carbimazole (5 mg daily). Results of her serial thyroid function tests are summarised in Table 1 and Figures 1a–c.

On 27 November 2021, the patient received a booster dose of the Pfizer-BioNTech SARS-CoV-2 vaccine. A few days after, she developed palpitations, hot flushes and diarrhoea. She was reviewed at the endocrinology outpatient unit on 14 December 2021, where she was still symptomatic and reported an unintentional 3 kg weight loss over the past 2 weeks, despite an increase in appetite and oral intake.

On physical examination, she was noted to be diaphoretic with a regular resting heart rate of 115 beats per minute. She had a tremor in her outstretched hands. She was otherwise normotensive and afebrile with oxygen saturations of 98% on room air. Her thyroid gland was diffusely enlarged, with no tenderness elicited on palpation. There were no signs of Graves' ophthalmopathy or dermopathy.

Laboratory investigations revealed a picture of thyrotoxicosis with a suppressed thyroid-stimulating hormone level of 0.008 µIU/ml in the setting of elevated free thyroxine (40.5 pmol/litre) and free triiodothyronine (16.2 pmol/litre) levels. A significant rise in thyroid-stimulating hormone receptor antibody level was also observed from a baseline of 2.8 IU/litre in October 2021 (pre-Pfizer-BioNTech SARS-CoV-2 vaccine booster dose) to 9.9 IU/litre in December 2021 (1 month post-Pfizer-BioNTech SARS-CoV-2 vaccine booster dose). The carbimazole dose was increased to 10 mg twice daily, resulting in clinical and biochemical improvement (Table 1). Following this episode, it was interesting to note that the patient required a larger carbimazole dose to render her clinically euthyroid, and her thyroid-stimulating hormone was still persistently suppressed despite higher doses of thionamide therapy when compared to her initial presentation with Graves' disease before her vaccine booster administration (Table 1).

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Table 1. Serial thyroid function tests and thyroid-stimulating hormone-receptor antibody levels

	Date	Thyroid-stimulating hormone (μIU/ml) (reference range 0.3–3)	Free thyroxine (pmol/litre) (reference range 11–18)	Free triiodothyronine (pmol/litre) (reference range 3.5–6.5)	Thyroid-stimulating hormone receptor antibody (IU/litre) (reference range 0.1–1.0)
At initial diagnosis	7 July 2019	<0.008	76.08	30.8	>40.0
On carbimazole treatment	7 September 2019	0.243	7.57	3.5	Not repeated
	30 November 2019	2.528	13.92	5.6	Not repeated
	4 May 2020	2.805	14.60	4.8	7.9
	9 November 2020	2.610	17.12	4.8	Not repeated
	11 January 2021	5.429	16.32	4.5	6.3
	23 June 2021	2.825	16.79	6.1	Not repeated
	13 October 2021	2.161	17.08	4.5	2.8
After SARS-CoV-2 vaccine booster dose (given 27 November 2021)	14 December 2021	0.008	40.50	16.2	9.9
	13 January 2022	0.011	28.10	8.7	Not repeated
	18 February 2022	0.009	22.60	6.5	Not repeated
	25 March 2022	0.096	22.27	6.3	6.6
	29 April 2022	0.019	19.12	5.2	Not repeated

woman with active Graves' disease. Before her vaccine booster was given, the patient was clinically and biochemically euthyroid on a stable low dose of antithyroid drug. However, following vaccine administration, she had a persistently suppressed thyroid-stimulating hormone level coupled with an increase in dose requirements for antithyroid drugs, suggesting aggravation of her pre-existing Graves' disease.

Discussion

The pathogenesis of Graves' disease is determined by the interaction of genetic, environmental and endogenous factors (Brix et al, 1998). Several infectious agents, including viruses, have been found to be associated with Graves' disease (Paluchamy, 2021).

Since the outbreak of the COVID-19 pandemic, there have been case reports of autoimmune diseases, including new onset or relapse of Graves' disease-related hyperthyroidism, being triggered by both SARS-CoV-2 infection and immunisation (Lui et al, 2021).

A case series by Chee et al (2022) suggested that new onset or relapse of Graves' disease was reported to occur within days (up to 38 days) of receiving the SARS-CoV-2 vaccine, especially the RNA-based vaccine.

There are a number of mechanisms by which the SARS-CoV-2 vaccine could cause new onset Graves' disease or exacerbation of the underlying thyroid autoimmunity. The nucleoside-modified mRNA encapsulated in lipid nanoparticles in the Pfizer-BioNTech COVID-19 vaccine may act as adjuvants and trigger an autoimmune or inflammatory syndrome induced by adjuvants in genetically predisposed individuals, as a result of immunostimulation via the T follicular helper cells and humoral responses (Bostan et al, 2022).

Kanduc and Shoenfeld (2020) suggested that molecular mimicry between the SARS-CoV-2 spike glycoprotein and human proteosomes may be another mechanism of autoimmune disease following COVID-19 vaccination.

The Moderna and Pfizer-BioNTech vaccines use mRNA coding for the SARS-CoV-2 S protein. The S protein binds to the angiotensin-converting enzyme-2 receptor, allowing the virus to enter the cell (Pujol et al, 2022). Rotondi et al (2021) showed that angiotensin-

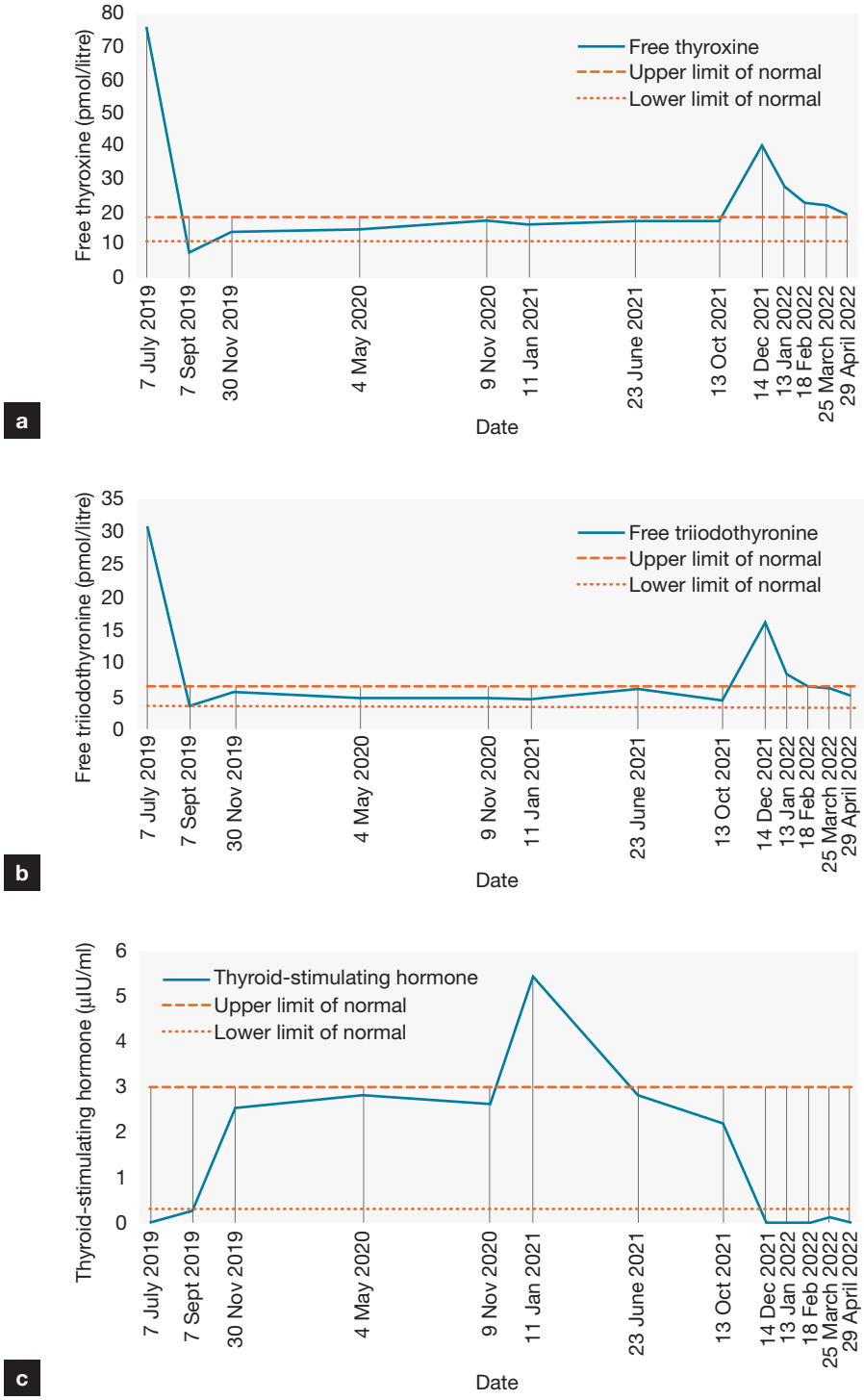

Figure 1. Thyroid function tests over time. a. Free thyroxine levels. b. Free triiodothyronine levels. c. Thyroid-stimulating hormone levels.

converting enzyme-2 receptors are expressed in thyroid follicular cells, making them a potential target for SARS-CoV-2 entry.

While most cases report relapsed and newly diagnosed Graves' disease following SARS-CoV-2 immunisation, this case highlights that vaccination can also aggravate pre-existing active Graves' disease, leading to a persistent increase in dose requirements of antithyroid drugs.

Oğuz et al (2022) suggested that SARS-CoV-2 vaccination (including repeat doses) should not be discouraged, as the benefit of immunisation against COVID-19 and the risk

Learning points

- While most cases report relapsed and newly diagnosed Graves' disease following SARS-CoV-2 immunisation, this case highlights that vaccination can also aggravate pre-existing active Graves' disease, leading to a persistent increase in dose requirements for antithyroid drugs.
- Physicians should remain vigilant for the potential development of thyrotoxicosis post-SARS-CoV-2 immunisation, even in patients without any significant risk factors, in order to make the correct diagnosis and provide timely management to prevent comorbidities of Graves' disease such as thyroid storm.
- Patients should be educated about the symptoms of thyrotoxicosis so they can seek early medical assistance.

of COVID-19 clearly outweigh the risks of vaccination. However, the authors stated that while further vaccinations appear to be safe in patients with SARS-CoV-2-vaccine-induced subacute thyroiditis, more evidence is required regarding SARS-CoV-2 vaccine-induced Graves' disease (Oğuz et al, 2022). Hence, physicians should have a high index of clinical suspicion for thyroid dysfunction after recent SARS-CoV-2 immunisation, in order to avoid delays in diagnosis and management (Goblirsch et al, 2021).

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