Graves' disease after COVID-19 vaccination

Dear Editor,

Case 1 was a 41-year-old man with a history of primary hyperthyroidism. At the time of diagnosis, thyroglobulin antibodies were elevated although no thyrotropin receptor antibodies (TRAB) were available. The patient was treated with carbimazole for 20 months. At the time of cessation of carbimazole in May 2020, thyroid function and TRAB levels were normal. The patient remained euthyroid until his first dose of the mRNA-1273 (Moderna) SARS-CoV-2 vaccine in May 2021. The following day, the patient developed generalised muscle aches and weakness, and noticed that he was more forgetful. This was followed 5 days later by tremors and palpitations for which he sought medical attention. A physical examination was unremarkable apart from fine hand tremors. Investigations showed recurrent primary hyperthyroidism with elevated TRAB consistent with Graves' disease (GD) (Table 1), for which carbimazole was restarted.

Case 2 was a 45-year-old woman with no history of thyroid disease who presented with chest tightness and palpitations 4 days after receiving the first dose of the BNT162b2 (Pfizer-BioNTech) SARS-CoV-2 vaccine. Two days after vaccination, she developed generalised body aches and fever (38°C) with no localising symptoms of infection, which subsequently spontaneously resolved. The patient had a normal thyroid function test 3 years ago and had no symptoms of hyperthyroidism before vaccination. Other than fine tremors of the hands, physical examination was unremarkable. Investigations

showed primary hyperthyroidism with elevated TRAB consistent with new-onset GD (Table 1) and she was started on carbimazole.

In both patients, there was no family history of thyroid disease, palpable goitre, thyroid acropachy, pretibial myxedema or signs of thyroid eye disease.

Although the development of primary hyperthyroidism following SARS-CoV-2 vaccination is increasingly recognised,¹ the aetiology is almost exclusively subacute thyroiditis—a benign and self-limiting disorder.¹⁻³ In contrast, there were only 2 reported cases of GD following SARS-CoV-2 vaccination to date, both of which occurred following administration of the BNT162b2 vaccine.⁴ In this report, Case 2 represented new-onset GD following administration of the BNT162b2 vaccine while in Case 1, administration of the mRNA-1273 vaccine likely triggered relapse of underlying GD. As GD is associated with potentially sight-threatening eye disease and has specific implications in pregnancy, its diagnosis carries far greater significance compared to subacute thyroiditis.

What would be the mechanism of new-onset GD following SARS-CoV-2 vaccination? The most likely aetiology in the described patients is the autoimmune/inflammatory syndrome induced by adjuvants (ASIA), a post-vaccination phenomenon due to a reaction to vaccine adjuvants in genetically predisposed individuals.¹ Both patients fulfilled the diagnostic criteria for ASIA—they were previously healthy, developed suggestive symptoms of fever, myalgia, weakness and cognitive

Table 1. Thyroid function and thyroid antibodies at time of diagnosis of Graves' disease following SARS-CoV-2 vaccination

	Case 1	Case 2	Reference range
fT4, pmol/L	48.2	45.1	12.7–20.3
TSH, mIU/L	<0.01	<0.005	0.70–4.28
TRAB, IU/L	3.85	5.75	<1.76
Thyroid peroxidase antibodies, IU/mL	Not available	0.3	<9.0
Ultrasound thyroid	Not available	Heterogeneous thyroid gland with increased vascularity A few sub-centimetre solid and cystic nodules are present	Not applicable

fT4: free thyroxine; TRAB: thyrotropin receptor antibodies; TSH: thyroid stimulating hormone

Table 2. Features of autoimmune/inflammatory syndrome induced by adjuvants (ASIA)¹

Major criteria	Minor criteria
Exposure to external stimuli (vaccination and immunisation procedures, infectious agents and pathogens, other adjuvants) prior to onset of clinical symptoms	Positivity for auto-antibodies
The development of at least 1 of the following symptoms: <ul style="list-style-type: none"> • Fever, dry mouth or other sicca syndrome-like symptoms • Muscle pain, weakness or myositis • Arthritis or arthralgia • Chronic fatigue, malaise and sleep disturbances • Cognitive defects including memory loss • Neurological manifestations 	Other clinical manifestations e.g. fibromyalgia and irritable bowel syndrome
Removal of the adjuvant leads to a full or at least partial recovery	Genetic predisposition e.g. specific human leukocyte antigen haplotype
Biopsy of involved organs	Personal or family history of autoimmune disease e.g. systemic sclerosis, multiple sclerosis

deficits following vaccination, and were positive for auto-antibodies¹ (Table 2). Both the BNT162b2 and mRNA-1273 vaccines contain polyethylene glycol lipid conjugates that may act as adjuvants and induce an immune response.¹ The short time interval between vaccination and development of hyperthyroidism is similar to other reports of vaccine-induced thyroiditis and could be due to a rapid peak in adjuvant concentration.¹

Another possible aetiology of post-vaccination GD is molecular mimicry with antigen exposure leading to cytokine release and an inflammatory response, as supported by cases of new-onset GD following SARS-CoV-2 infection.^{5,6}

Many unanswered questions remain on the natural history and prognosis of GD following SARS-CoV-2 vaccination. Based on the criteria for ASIA syndrome, a full or partial recovery is expected following removal of the adjuvant. As such, whether patients require a shorter duration of thionamide treatment with closer thyroid function monitoring to avoid development of hypothyroidism remains to be ascertained. Both patients asked whether they should proceed to receive the subsequent doses of the vaccine. Although much is still unknown, both patients eventually decided to complete their vaccination course after weighing the risks and benefits of vaccination. Both the mRNA-1273 and BNT162b2 vaccines have been shown to be generally safe with high efficacies of 94.6% and 94.1%, respectively.^{7,8} Although the risk of worsening hyperthyroidism exists, this is likely to be transient and can be mitigated with treatment.

In conclusion, GD is an important potential complication of SARS-CoV-2 vaccination. In patients with known history of GD in remission, clinicians should be vigilant for relapse of GD following SARS-CoV-2 vaccination.

In addition, clinicians should consider hyperthyroidism as a differential diagnosis in all patients presenting with suggestive symptoms following SARS-CoV-2 vaccination.

REFERENCES

1. Bragazzi NL, Hejly A, Watad A, et al. ASIA syndrome and endocrine autoimmune disorders. *Best Pract Res Clin Endocrinol Metab* 2020;34:101412.
2. İremli BG, Şendur SN, Ünlütürk U. Three cases of subacute thyroiditis following SARS-CoV-2 vaccine: postvaccination ASIA syndrome. *J Clin Endocrinol Metab* 2021;106:2600-5.
3. Şahin Tekin M, Şaylısoy S, Yorulmaz G. Subacute thyroiditis following COVID-19 vaccination in a 67-year-old male patient: a case report. *Hum Vaccin Immunother* 2021;17:4090-2.
4. Vera-Lastra O, Ordinola Navarro A, Cruz Domiguez MP, et al. Two cases of Graves' disease following SARS-CoV-2 vaccination: An autoimmune/inflammatory syndrome induced by adjuvants. *Thyroid* 2021;31:1436-9.
5. Mateu-Salat M, Urgell E, Chico A. SARS-CoV-2 as a trigger for autoimmune disease: report of two cases of Graves' disease after COVID-19. *J Endocrinol Invest* 2020;43:1527-8.
6. Harris A, Al Mushref M. Graves' Thyrotoxicosis following SARS-CoV-2 infection. *AACE Clin Case Rep* 2021;7:14-6.
7. Skowronski DM, De Serres G. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2021;384:1576-7.
8. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384:403-6.

Marvin Wei Jie Chua ¹MRCP (UK)

¹ Endocrinology Service, Department of General Medicine, Sengkang General Hospital, Singapore

Correspondence: Dr Marvin Wei Jie Chua, Endocrinology Service, Department of General Medicine, Sengkang General Hospital, 110 Sengkang East Way, Singapore 544886.
Email: marvin.chua.w.j@singhealth.com.sg