

A case of Graves' disease and type 1 diabetes mellitus following SARS-CoV-2 vaccination

Armando Patrizio ^a, Silvia Martina Ferrari ^b, Alessandro Antonelli ^{c,*}, Poupak Fallahi ^d

^a Department of Emergency Medicine, Azienda Ospedaliero-Universitaria Pisana, Italy

^b Department of Clinical and Experimental Medicine, University of Pisa, Italy

^c Department of Surgery, Medical and Molecular Pathology and of Critical Area, University of Pisa, Italy

^d Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Italy

* Corresponding author. Department of Surgery, Medical and Molecular Pathology and of Critical Area, University of Pisa, School of Medicine, Via Savi, 10, I-56126, Pisa, Italy.

Abstract

Autoimmune diseases, including autoimmune endocrine diseases (AIED), are thought to develop following environmental exposure in patients with genetic predisposition. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and vaccines against it could represent new environmental triggers for AIED. We report a patient, with history of vitiligo vulgaris and 8 years of type 2 diabetes, who came to our institution because of fever, weight loss, asthenia and thyrotoxicosis occurred 4 weeks later the administration of BNT162B2 (Pfizer-BioNTech) SARS-CoV-2 vaccine. Clinical, biochemical and instrumental work-up demonstrated Graves' disease and autoimmune diabetes mellitus. The occurrence of these disorders could be explained through different mechanism such as autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome), mRNA "self-adjuvant" effect, molecular mimicry between human and viral proteins and immune disruption from external stimuli. However further studies are needed to better understand the underlying pathogenesis of AIED following SARS-CoV-2 vaccine.

1. The case report

A 52-year-old male patient with a history of vitiligo vulgaris and 8 years type 2 diabetes mellitus being treated with oral antidiabetic agents with good glycemic control (glycated hemoglobin

[HbA1c] 53 mmol/mol 3 months before), came to the emergency department for the onset of night fever (T max 38 °C), weight loss of 7 kg and profound asthenia lasting for about 1 month. These symptoms emerged 4 weeks after the administration of the second dose of the BNT162B2 SARS-CoV-2 (Pfizer-BioNTech) vaccine. No previous SARS-CoV-2 infection was documented. On the physical examination, he had mild diffuse thyromegaly without tenderness neither signs or symptoms of Graves' ophthalmopathy (GO). The laboratory tests revealed an overt hyperthyroidism (thyrotropin [TSH] <0.004 mIU/L [0.4–4.00], free triiodothyronine [fT3] 15 ng/L [2.7–5.7], free thyroxine [fT4] 5.56 ng/dL [0.7–1.7]), with positivity for organ-specific circulating auto-antibodies (thyrotropin receptor antibodies [TRAb] 6.48 IU/L [0–1.49], thyroglobulin antibodies [TgAb] 30 IU/mL [0–30], thyroperoxidase antibodies [TPOAb] 21 IU/mL [0–10]) and the characteristic ultrasound features for Graves' disease were detected i.e. enlarged thyroid gland with heterogeneous echotexture, increased vascularization and "Thyroid Inferno" pattern on color Doppler. No history of thyroid diseases was documented till this time. Therapy with Methimazole and Atenolol was then set with progressive improvement of symptoms, disappearance of fever and normalization of thyroid hormones.

At the same time, the blood chemistry tests revealed poor control of glycemic values and a significantly increased level of HbA1c (87 mmol/mol [20–38]). In the light of the clinical history and the predisposition for autoimmunity (vitiligo, Graves' disease), the islet-specific pancreatic autoantibodies against glutamic acid decarboxylase 65 (GAD65Ab) were measured, for the first time in this patient, and they turned frankly positive (61.2 IU/mL [0–1]), associated with a very low serum values of c-Peptide (1 ng/mL [1–3.5]). It should be emphasized that the underlying state of thyrotoxicosis also could have contributed to the increase in blood glucose. According to these results, autoimmune diabetes mellitus was diagnosed, and the patient was treated with insulin analogues to restore glycemic control.

2. Discussion

The widespread use of mRNA vaccines against SARS-CoV-2 has quickly revealed their possible side effects such as fever, fatigue, headache, muscle and joint pain or anaphylaxis [1]. Moreover, cases with immune-mediated [2] or even with auto-immune pathophysiology have been also described [3,4].

Two recent reports [5,6] describe the first four cases of Graves' disease following the administration of the BNT162B2 SARS-CoV-2 (Pfizer-BioNTech) vaccine.

According to Vera-Lastra and colleagues [5], the two cases of Graves' disease they reported, fully satisfy the “autoimmune/inflammatory syndrome by adjuvants” (ASIA syndrome) criteria as the disease occurred in previously healthy individuals, after exposure to the vaccine and was associated with the appearance of organ-specific serum autoantibodies. The authors pointed out that the polyethylene glycol (PEG) lipid conjugates, which stabilize the nanoparticles of the vaccine, may act as adjuvants and induce the autoimmune reactions, and not only anaphylaxis as already described [7]. Furthermore, mRNA seems to have self-adjuvants properties able to activate strong and long-protective adaptive immune responses through tumor necrosis factor- α (TNF- α), interferon- α (IFN- α) and other cytokines secretion by immune cells, while polypeptide and protein based vaccines need extra adjuvants to achieve a similar goal [8].

In fact, vaccine adjuvants, in genetically susceptible and predisposed subjects, have shown the potential to induce serious adverse reactions, due to the activation of autoimmune cascades and

pathways, by impairing/disrupting the immunological balance of the host, fostering polyclonal activation of B lymphocytes, by molecular mimicry or other similar etiopathogenetic mechanisms [9]. Among the side effects, even autoimmune endocrine dysfunctions have been reported including two cases of chronic lymphocytic thyroiditis, also known as Hashimoto's thyroiditis (HT) [10,11]. These phenomena and reactions have been comprehensively collected together under the term of “autoimmune/inflammatory syndrome by adjuvants” (ASIA syndrome) coined by Shoenfeld and Agmon-Levin in 2011 [9].

Another important aspect to consider is the similarity of the spike glycoprotein of SAR-CoV2 with a large heptapeptide human protein [12], suggesting that the molecular mimicry hypothesis could be a potential mechanism underlying the autoimmune reactions induced by the vaccine in genetically predisposed subjects [13], [14], [15].

Finally, the interesting feature of the case we report is not only the appearance of a newly diagnosed Graves' disease, but also the conversion of pre-existing type 2 diabetes mellitus, into Type 1 autoimmune diabetes, following the vaccine against SARS-CoV-2. This was supported by positive islet-specific pancreatic autoantibodies (GAD65Ab) and very low levels of C-peptide, demanding a switch from oral antidiabetic therapy to insulin therapy to normalize the glycemic profile.

To the best of our knowledge, so far this is the fifth description of Graves' disease with a new diagnosis of type 1 autoimmune diabetes mellitus following SARS-CoV-2 vaccination. This represents a novel phenomenon in this setting.

Since vaccination against the SARS-CoV-2 is the milestone of the prevention of the infection spread, prospective studies are needed to define the incidence and quantify the clinical impact of the development of autoimmune diseases associated to SARS-CoV-2 vaccine and to elucidate the underlying pathogenetic mechanisms.

Author statement

Armando Patrizio: Conceptualization, Investigation, Writing - Original Draft and Review & Editing. Silvia Martina Ferrari: Formal analysis, Writing - Review & Editing. Alessandro Antonelli: Conceptualization, Investigation, Writing - Review & Editing, Supervision. Poupak Fallahi: Writing-Review & Editing, Supervision.

References

1. Castells M.C., Phillips E.J. Maintaining safety with SARS-CoV-2. *N. Engl. J. Med.* 2021;384:643–649. doi: 10.1056/NEJMra2035343.
2. Dias L., Soares-Dos-Reis R., Meira J., Ferrao D., Ribeirinho Soares P., Pator A., et al. Cerebral venous thrombosis after BNT162b2 mRNA SARS-CoV-2 vaccine. *J. Stroke Cerebrovasc. Dis.* 2021;30 doi: 10.1016/j.jstrokecerebrovasdis.2021.105906.

3. Bril F., Al Diffalha S., Dean M., Fetting D.M. Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: causality or casualty? *J. Hepatol.* 2021;75:222–224. doi: 10.1016/j.jhep.2021.04.003.
4. Vuille-Lessard E., Montani M., Bosch J., Semmo N. Autoimmune hepatitis triggered by SARS-Cov-2. *J. Autoimmun.* 2021;123 doi: 10.1016/j.jaut.2021.102710.
5. Vera-Lastra O., Ordinola Navarro A., Pilar Cruz Domigiez M., Medina G., Sanchez Valadez T.I., Jara L.J. Two cases of Graves' disease following SARS-CoV-2 vaccination: an autoimmune/inflammatory syndrome induced by adjuvants. *Thyroid.* 2021;136:168–186. doi: 10.1089/thy.2021.0142.
6. Zettining G., Krebs M. Two further cases of Graves' disease following SARS-CoV-2 vaccination. *J. Endocrinol. Invest.* 2021;1–2. doi: 10.1007/s40618-021-01650-0.
7. Garvey L.H., Nassr S. Anaphylaxis to the first COVID-19 vaccine: is polyethylene glycol (PEG) the culprit. *Br. J. Anaesth.* 2021;126:106–108. doi: 10.1016/j.bja.2020.12.020.
8. Xu S., Yang K., Li R., Zhang L. mRNA vaccine era-mechanisms, drug platform and clinical prospection. *Int. J. Mol. Sci.* 2020;21 doi: 10.3390/ijms21186582.
9. Shoenfeld Y., Agmon-Levi N. 'ASIA' – autoimmune/inflammatory syndrome induced by adjuvants. *J. Autoimmun.* 2011;36:4–8. doi: 10.1016/j.jaut.2010.07.003.
10. Watad A., David P., Brown S., Shoenfeld Y. Autoimmune/inflammatory syndrome induced by adjuvants and thyroid autoimmunity. *Front. Endocrinol.* 2017;7 doi: 10.3389/fendo.2016.00150.
11. Bragazzi N.L., Hejly A., Watad A., Adawi M., Amital H., Shoenfeld Y. ASIA syndrome and endocrine autoimmune disorders. *Best Pract. Res. Clin. Endocrinol. Metabol.* 2020;34 doi: 10.1016/j.beem.2020.101412.
12. Kanduc D., Shoenfeld Y. Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. *Immunol. Res.* 2020;68:310–313. doi: 10.1007/s12026-020-09152-6.
13. Davies T.F. Infection and autoimmune thyroid disease. *J. Clin. Endocrinol. Metab.* 2008;93:674–676. doi: 10.1210/jc.2008-0095.
14. 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;43:1527–1528. doi: 10.1007/s40618-020-01366-7.
15. Antonelli A., Ferrari S.M., Corrado A., Di Domenicantonio A., Fallahi P. Autoimmune thyroid disorders. *Autoimmun. Rev.* 2015;14:174–180. doi: 10.1016/j.autrev.2014.10.016.