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## Worsening of Graves' ophthalmopathy after SARS-CoV-2 mRNA vaccination

### ARTICLE INFO

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### ABSTRACT

More reports are documenting how vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) could represent new external triggers for autoimmune endocrine diseases (AIED) in patients with individual predisposition. We report two cases of Graves' Ophthalmopathy (GO) recrudescence few days after the administration of BNT162B2 (Pfizer-BioNTech) SARS-CoV-2 vaccine. Even if causality relationship cannot be excluded, the development of these events could be explained through immune mediated mechanism such as the autoimmune/inflammatory syndrome induced by adjuvants (ASIA). While further investigations are necessary to improve our knowledge of the underlying pathogenesis of these phenomena, caution may be warranted when vaccinating individuals with known autoimmune diseases.

### Dear Editor

Since the end of 2020, vaccines against SARS-CoV-2 have been released and predictable adverse events such as fever, fatigue, headache, muscle and joint pain or anaphylaxis have been documented [1]. However, emerging evidence of autoimmune diseases following immunization with certain COVID-19 vaccines is what sparked the medical community. [2]

Here we report two cases of Graves' ophthalmopathy recrudescence following vaccination with BNT162B2 SARS-CoV-2 vaccine (Pfizer-BioNTech).

A 58-year-old woman with a three-year history of Graves' disease (GD) and Graves' ophthalmopathy (GO) (Clinical Activity Score [CAS] 3/7 at the diagnosis, no proptosis - 19-19 mm OO, base 102 at exophthalmometer-), came to our department due to worsening of GO (chemosis, redness of eyelids and conjunctiva, periorbital edema, pain and foreign object sensation in the eyes and diplopia, CAS 6/10) 3 days after receiving the second dose of BNT162B2 SARS-CoV-2 vaccine. Laboratory test revealed euthyroidism on hormone replacement therapy with levothyroxine (thyrotropin [TSH] 1.170 mIU/L [0.4–4.00], free triiodothyronine [fT3] 3.54 ng/L [2.7–5.7], free thyroxine [fT4] 1.26 ng/dL [0.7–1.7]) and positivity for thyrotropin receptor antibodies (TRAb) of 6.82 IU/L [0–1.5]. No previous Coronavirus disease 2019 (COVID-19) was reported. Two years before she underwent to definitive therapy for GD with radioactive iodine (131-I) and she then received 4.5 g of intravenous Methylprednisolone for GO which remained stable till the SARS-CoV-2 vaccination. Administration of Teprotumumab is planned.

A 43-year-old man, with no history of COVID-19, came to our attention because of recrudescence of moderate-to-severe and active GO (CAS 8/10, with proptosis of OD 28 mm and OS 30 mm, base 109 at exophthalmometer) two weeks after the administration of BNT162B2 SARS-CoV-2 vaccine. He also showed abduction deficit with diplopia, bilateral exposure keratopathy due to lagophthalmos and high risk of eye-ball subluxation and dysthyroid optic neuropathy (DON). The thyroid function test resulted normal (TSH 2.316 mIU/L [0.4–4.00], fT3 3.4 ng/L [2.7–5.7], fT4 0.76 ng/dL [0.7–1.7]), but TRAb were elevated

(20.7 IU/L [0–1.5]). One year before, the patient was diagnosed with GD, treated with Methimazole, and GO (CAS 4/7, proptosis of OD 28 mm, OS 28.5 mm, base 109 at exophthalmometer). The patient has already received specific therapy with 6 g of intravenous Methylprednisolone (12 months before) and external orbital radiation (20 Gy, 10 months before) with subjective amelioration.

According to previous reports, the “autoimmune/inflammatory syndrome by adjuvants” (ASIA syndrome) is invoked as the most plausible explanation for these immune mediated phenomena, including the new cases of GD emerged following mRNA vaccine against SARS-CoV-2 [3–5].

In fact, vaccine adjuvants, in genetically susceptible and predisposed subjects, can lead to severe adverse events, due to the activation of autoimmune cascades and pathways [6]. In particular, the BNT162B2 SARS-CoV-2 vaccine contains polyethylene glycol (PEG) lipid conjugates to stabilize the nanoparticles, and PEG may act as adjuvant inducing autoimmune reactions [4]. Furthermore, the mRNA has self-adjuvants properties and it can elicit strong and long-protective adaptive immune responses through the synthesis by immune cells of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\alpha$  (IFN- $\alpha$ ) and other cytokines, while polypeptide and protein-based vaccines need extra adjuvants to achieve a similar goal [7].

Rubinstein has reported a case of new onset GO after 3 days later the administration of the second dose of BNT162B2 SARS-CoV-2 vaccine in a female patient with history of stable GD treated with radioactive iodine more than 10 years before [8]. As in that case, also our patients showed normal thyroid function, elevation of TRAb levels and no new alternative triggering environmental factors such as novel hyperthyroidism flare, pregnancy status, smoking status, or any recent surgery. Moreover, their GO were stable as documented by several follow-up visits at our clinic.

Coincidental occurrence of GO and the vaccine administration cannot be excluded, but, just as the previous cases of autoimmune thyroiditis following the SARS-CoV-2 immunization, the close temporal relationship between these two events raises questions about the

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potential immune stimulation elicited by the vaccine injection in a predisposed person.

To date these are the first descriptions of GO worsening following the administration of the BNT162B2 SARS-CoV-2 vaccine.

Finally, although the tremendous benefits brought out for the public health by the SARS-CoV-2 vaccination, all the collected cases of autoimmune reactions, inclusive of autoimmune thyroid diseases and, now of GO, should raise health care providers' caution of patients affected by autoimmune disease.

## Disclosure

There are no funding sources associated with the writing of this manuscript. Written consent for publication was obtained from the patient.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Armando Patrizio<sup>a</sup>, Silvia Martina Ferrari<sup>b</sup>, Alessandro Antonelli<sup>c,\*</sup>,  
Poupak Fallahi<sup>d</sup>

<sup>a</sup> Department of Emergency Medicine, Azienda Ospedaliero-Universitaria  
Pisana, Italy

<sup>b</sup> Department of Clinical and Experimental Medicine, University of Pisa,  
Italy

<sup>c</sup> Department of Surgery, Medical and Molecular Pathology and of Critical  
Area, University of Pisa, Italy

<sup>d</sup> Department of Translational Research and New Technologies in Medicine  
and Surgery, University of Pisa, Italy

\* Corresponding author at: Immuno-Endocrine Section of Internal  
Medicine, Medicine, Endocrinology, Clinical Pathology, Laboratory of  
Primary Human Cells, Department of Surgery, Medical and Molecular  
Pathology and of Critical Area, University of Pisa, School of Medicine,  
Via Savi, 10, I-56126 Pisa, Italy.

E-mail addresses: [silvia.ferrari@unipi.it](mailto:silvia.ferrari@unipi.it) (S.M. Ferrari), [alessandro.antonelli@unipi.it](mailto:alessandro.antonelli@unipi.it) (A. Antonelli), [poupak.fallahi@unipi.it](mailto:poupak.fallahi@unipi.it) (P. Fallahi).