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CASE REPORT
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A Case of Concomitant Diffuse Sclerosing Variant of Papillary Thyroid Carcinoma and Graves' Disease with Ophthalmopathy Appeared After Coronavirus Disease 2019 Vaccine

ABSTRACT

It is known that the risk of developing thyroid carcinoma is increased in patients with Graves' disease (GD). Some reports document how severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination or infection could represent new external triggers for autoimmune thyroid disease such as GD in patients with individual predisposition. We describe GD and Graves' ophthalmopathy (GO) in a 27-year-old male patient 15 days after inactivated coronavirus disease 2019 (COVID-19) vaccine. Given the ophthalmopathy and uncontrolled hyperthyroidism, a thyroidectomy decision was made. Histopathological examination revealed a diffuse sclerosing variant of papillary thyroid carcinoma (DSV-PTC), and GD was detected in the parenchyma of non-neoplastic thyroid tissue. Various environmental, genetic, and epigenetic factors that initiate the development of GD are known, and cases of GD after COVID-19 vaccination have also been reported. However, the etiology of GD after COVID-19 vaccination has not been fully elucidated in the literature. In addition, the DSV-PTC is a rare subtype of papillary thyroid carcinoma, and its association with GD has been reported in very few cases. Interestingly, we report for the first time a case of DSV-PTC associated with GD histopathologically following inactivated COVID-19 vaccine. The molecular mechanisms of extremely rare co-existence in our case have aroused curiosity and need to be clarified by further studies.

Keywords: Diffuse sclerosing subtype of papillary thyroid carcinoma, Graves' disease, Graves' ophthalmopathy, COVID-19 vaccine

Introduction

Graves' disease (GD) is the most frequent cause of hyperthyroidism. Multiple factors, such as environmental, genetic, and immunological factors, may cause the development of GD. Several cases of GD with or without Graves' opthalmology (GO) in individuals who had any kind of vaccine against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) were reported.[1] Bostan et al[2] documented 7 patients with recurrent or newly diagnosed GD after coronavirus disease 2019 (COVID-19) vaccination, and one of the newly diagnosed GD associated with an inactive COVID-19 vaccine was presented. Additionally, the same authors described a case developing GD and unilateral GO with the co-incidental classic subtype of papillary thyroid carcinoma (PTC) triggered by COVID-19 messenger ribonucleic acid (mRNA) vaccination.[2]

The prevalence of thyroid cancer in GD is variable, with rates of up to 21.1%.[3] Thyroid ultrasonography for the diagnosis of GD increases the chance of noticing thyroid nodules, and it is reported that the thyroid cancer risk rises with concomitant nodular disease.[4] Belfiore et al[5] showed that the malignancy rate in patients with GD and palpable thyroid nodules ranged from 2.3% to 45.8% but only in approximately 5% of the general population. In addition, increased aggressiveness of thyroid cancer has been demonstrated in GD patients than in those without GD.[6] In the literature, certain histological subtypes, such as tall cell and diffuse sclerosing variant (DSV), are characterized by more aggressive behavior in patients with GD.[7] Herein, we report a case of GD with a DSV-PTC and ophthalmopathy after an inactivated COVID-19 vaccine.

Case Presentation

A 27-year-old male without a history of any thyroid disorder presented with palpitations, heat intolerance, tremor, sweating, weight loss of 5 kg, and bilateral exophthalmos 15 days after

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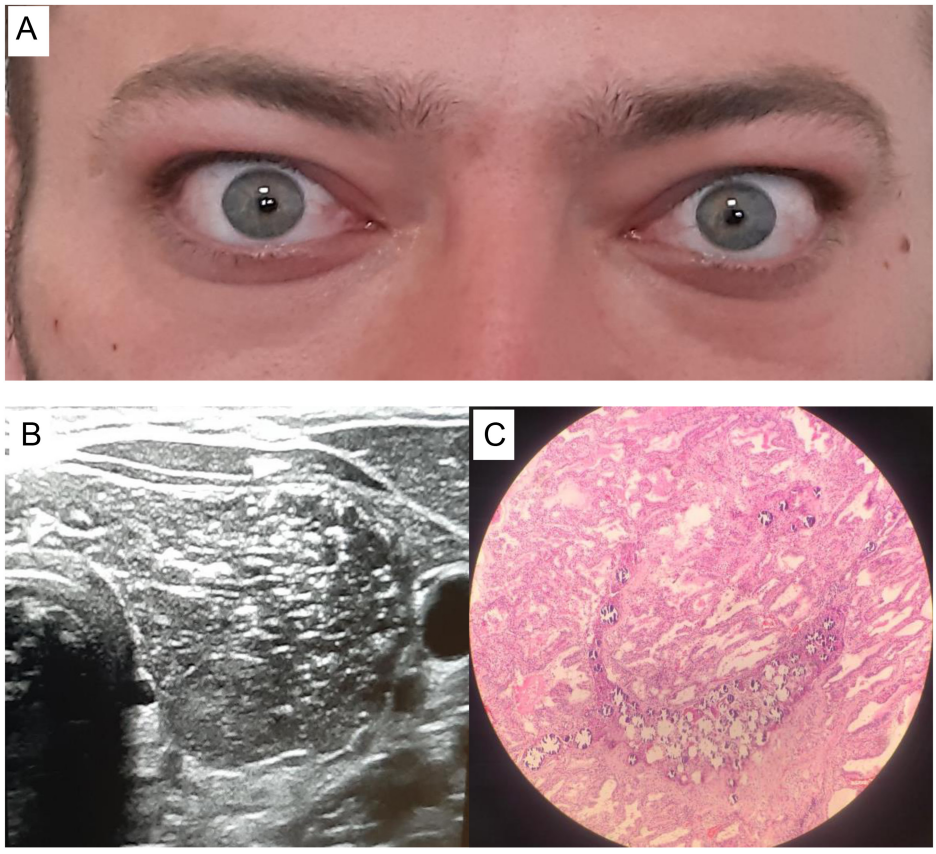

Figure 1. (A) Proptosis, mild periorbital edema, and 1+ chemosis seen in both eyes. (B) Thyroid ultrasonography of the case showing an enlarged left lobe with diffuse punctate areas that were relatively hyperechoic among hypoechoic parenchyma. (C) Magnified view of an area of a DSV-PTC: there is a diffuse infiltration of thyroid tissue with bands of fibrous tissue, lymphocytic infiltrate, and numerous psammoma bodies. DSV-PTC, diffuse sclerosing variant of papillary thyroid carcinoma.

receiving the first dose of inactivated COVID-19 vaccine (CoronoVac®) September 8, 2021. There was no documented SARS-CoV-2 infection before the onset of the symptoms. Complaints of proptosis, dryness, and orbital pain started 6 days after the first vaccine administration and gradually increased. Although he was a chronic smoker, his eyes were completely normal before the vaccine.

On physical examination, his blood pressure was 120/70 mmHg, heart rate 103 beats per minute, weight 65 kg, height 177 cm, and body mass index 20.7 kg/m^2. The thyroid gland was diffusely enlarged, with no palpable thyroid nodules and cervical lymph nodes. There was mild-to-moderately active GO with a clinical activity score of 3 in both eyes (Figure 1A). Skin examination was unremarkable, with no erythema and pretibial myxedema. Cardiac examination was normal except for tachycardia.

MAIN POINTS

- Diffuse sclerosing variant is an uncommon subtype of papillary thyroid carcinoma, and it is the first case after a vaccine.
- Both severe acute respiratory syndrome coronavirus 2 vaccination and infection trigger several autoimmune diseases such as Graves' disease.
- This article is interesting to a broad audience because the molecular mechanisms of extremely rare co-existence, in our case, have aroused curiosity.

The thyroid function tests were as follows: free thyroxine 5.69 ng/dL [normal range (NR): 0.58-1.38 ng/dL], free triiodothyronine 20 pg/mL (NR: 2.13-4.5 pg/mL), and thyroid-stimulating hormone (TSH) <0.008 µIU/mL (NR: 0.38-5.33 µIU/mL). Anti-thyroperoxidase and anti-thyroglobulin antibodies were undetectable. The TSH receptor antibody was 13.61 U/L (<1.5). The erythrocyte sedimentation rate, complete blood count, and serum C-reactive protein level were normal. Thyroid ultrasonography revealed a bilaterally enlarged thyroid gland with no nodules. In addition, in the left lobe, there were diffuse punctate areas that were relatively hyperechoic among hypoechoic parenchyma (Figure 1B) on ultrasonography, and an increased diffuse activity uptake was observed on a technetium scan.

His clinical and laboratory findings supported the diagnosis of GD. Initially, the patient was started on 20 mg methimazole, and for symptomatic relief, 40 mg propranolol daily. Doses were increased to obtain euthyroidism. After 3 months of the initial treatment, SARS-CoV-2 infection was detected and was treated symptomatically (Figure 2). Despite a high-dose anti-thyroid agent, the patient still had not achieved euthyroid levels, and so the ophthalmopathy worsened increasingly. Given the ophthalmopathy, a thyroidectomy decision was made.

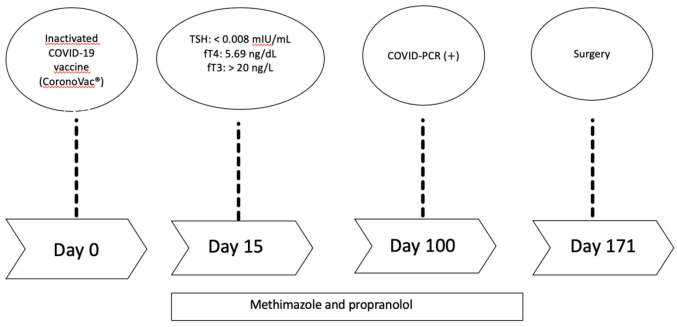

Figure 2. Timeline of the patient.

Histopathological examination revealed fibrotic bands throughout the thyroid containing multiple psammoma bodies arranged in large clusters, as well as diffuse involvement of classical PTC with papillary, solid, and follicular patterns, as suggested by DSV-PTC in both lobes and isthmus (Figure 1C). Due to hyperplastic changes of follicles, fibrosis could not be seen easily on a low-power field. There were also 2 metastatic lymph nodes in the left lobe and isthmus. GD was detected in the parenchyma of non-neoplastic thyroid tissue.

A written informed consent form was obtained from the patient for the publication of this case report.

Discussion

We described a case of concomitant DSV-PTC and GD with ophthalmopathy after 1 dose of an inactivated COVID-19 vaccine. Thyroid disorders, such as GD, and subacute thyroiditis, have been documented following the administration of all types of COVID-19 vaccines or COVID-19 infection.[2,8] It has also been identified in a case with GD and coincidental PTC after COVID-19 mRNA vaccination.[2]

Although the incidence of PTC in patients with GD varies, some studies support that PTC with GD is more aggressive than in euthyroid subjects.[7] Possible mechanisms to explain this aggressive pattern are still unclear. Autoimmunity and inflammation may be explanatory factors for thyroid cancer in patients with GD. The prevalence of DSV-PTC in GD has not been clearly documented. Boutzios et al[7] found that the incidence of DSV-PTC was not different between PTC patients with and without GD [4 (6.6%) and 19 (3.7%), respectively]. They have also shown that aggressive subtypes of PTC were more frequent in nodular micro-PTC in GD patients.[7] A study in a cohort of 182 non-nodular GD and PTC patients by Yoon et al[4] demonstrated 7 case subtypes of PTC were found only in the non-nodular GD group: 3 tall cell variant PTC cases (1.6%), 1 oncocytic variant PTC case (0.5%), 2 solid variant PTC cases (1.1%), and 1 DSV-PTC case (0.5%). Although the infiltration of lymphocytes and the presence of atypical follicular cells complicate the diagnosis of DSV-PTC, it is usually characterized by diffuse enlargement of the thyroid gland without the formation of a predominant nodular lesion. In our report, we present an interesting case of DSV-PTC associated with GD in a young male patient without thyroid nodules at the time of diagnosis.

Several mechanisms have been suggested to clarify the existence of thyroid dysfunction following the SARS-CoV-2 vaccine. Autoi mmune/inflammatory syndrome induced by vaccine adjuvants was first proposed by Shoenfeld and Agmon-Levin[9] in 2011. Adjuvants in vaccines enhance and trigger immune responses. One of these adjuvants is aluminium salt which is proposed to react with the thyroid gland by activating several immune pathways.[10] The inactivated COVID-19 vaccine (CoronoVac) contains this salt as an adjuvant to induce the immune response.[10] The second mechanism may be due to the molecular similarity between the spike protein of SARS-CoV 2 and tissue proteins.[11] This mimicry is a robust autoimmune response, especially in the thyroid gland.[12] Another potential mechanism by which COVID-19 vaccines exacerbate thyroid autoimmunity is an activation of the angiotensin-converting enzyme-2 receptors on the thyroid gland directly.[13] Interestingly, Sigrist et al[14] recently reported that SARS-CoV-2 may use integrins as cell receptors in 1 or more hosts. In addition, the plasma membrane receptor integrin avb3 is expressed in many tumors, and there is increasing data on the significant role of integrin avb3-mediated effects of thyroid hormones on the regulation of growing tumors.[15] The activation of integrin avb3 by the excessively high T4 levels of GD, leading to carcinogenesis, may explain this co-existence in this case. Although PTC has an indolent course, the patient's timeline gives rise to thought and an association between the vaccine and both GD and thyroid cancer beyond coincidence. Even if there is a coincidence, the patient may be had an occult thyroid malignancy for years.

To the best of our knowledge, our report describes the first case of concomitant DSV-PTC and GD with bilateral GO after inactivated COVID-19 vaccine. In our case, it is necessary to elucidate the molecular mechanisms that explain this surprising co-existence.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

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Declaration of Interests: The authors have no conflict of interest to declare.

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