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CASE REPORT
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Unusual Clinical Presentation of a Post-Severe Acute Respiratory Syndrome Coronavirus-2 Graves' Disease

ABSTRACT

Severe acute respiratory syndrome coronavirus-2 could act as a trigger of latent or new-onset auto-immunity. There have been reports of subacute thyroiditis, hypothyroidism or thyrotoxicosis, and Graves' disease. We describe an unusual case of a 48-year-old woman with a history of coronavirus disease 2019 infection 4 months before presenting abdominal distension and edema of the lower limbs, atrial fibrillation, and exophthalmos. The thyroid analysis revealed hyperthyroidism (thyroxine = 12.8 uIU/mL; thyroid-stimulating hormone = 0.008 uIU/mL). The transthoracic cardiac echography revealed dilated cardiomyopathy with a left ventricular ejection fraction of 54% and dilatated inferior vena cava and hepatic veins. Cardiac magnetic resonance imaging showed biventricular dilatation with left ventricular ejection fraction 29% and no ischemic necrosis or myocarditis sequelae. A neck ultrasound showed a homogeneous hypervascularized goiter; the radionuclide thyroid scanning showed a thyroid in place, with increased uniform tracer uptake. Graves' disease was diagnosed with positive anti-thyroid-stimulating hormone receptors antibodies at 35 IU/mL and anti-thyroid peroxidase antibodies at 312 IU/mL. The patient received treatment intravenous then oral furosemide besides 30 g of thiamazole, daily with Propranolol 40 mg/day. Six months later, the patient had radioiodine therapy. The ophthalmopathy, the goiter, and ascites regressed. Based on the pathophysiology of severe acute respiratory syndrome coronavirus-2 infection and invasion of the thyroid gland and many similar case reports of post-severe acute respiratory syndrome coronavirus-2 infection auto-immune diseases and endocrinopathies, we suggest that clinicians should keep an eye on thyroid function in the acute phase for coronavirus disease 2019 patients and during convalescence to diagnose hyperthyroidism before the onset of complications and control reversibility.

Keywords: COVID-19, Graves' disease, thyroid

Introduction

Since the outbreak of coronavirus disease 2019 (COVID-19), publications on COVID-19-related auto-immune diseases exploded, and this suggests that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) might be a trigger of latent or new-onset auto-immunity. Concerning thyroid disease, there have been case reports of subacute thyroiditis, hypothyroidism or thyrotoxicosis, and Graves' disease.

Case Presentation

We herein report the case of a 48-year-old woman with a history of a mild form of COVID-19 infection 4 months ago with no oxygen requirements nor hospitalization. Who showed up to the emergency ward with symptomatology, evolving for 1 week, consisting of abdominal distension associated with edema of the lower limbs and dyspnea on exertion in a context of uncounted weight loss with no fever. She reported that she noted a weight loss and changes in her looks including her eyes and a cervical mass during the last month.

The physical examination found a bilateral and slightly asymmetric exophthalmos (Figure 1A), a body mass index of 20, a heart rate of 130 bpm with persistent atrial fibrillation on the electrocardiogram, and blood pressure of 100/60 mmHg. The cardiac auscultation was normal. A homogeneous goiter with thrill was palpated (Figure 1B). Abdominal distension and edema of the lower limbs were present (Figure 1C). The skin, joint, and neurological examinations were without abnormalities.

The biological exploration found microcytic hypochromic anemia at 9.5g/dL, hypoalbuminemia at 27 g/L, hypocholesterolemia at 35 mmol/L, and calcemia at 2.68 mmol/L. There was no hepatic cytolysis or cholestasis, and prothrombin and creatinine levels were normal.

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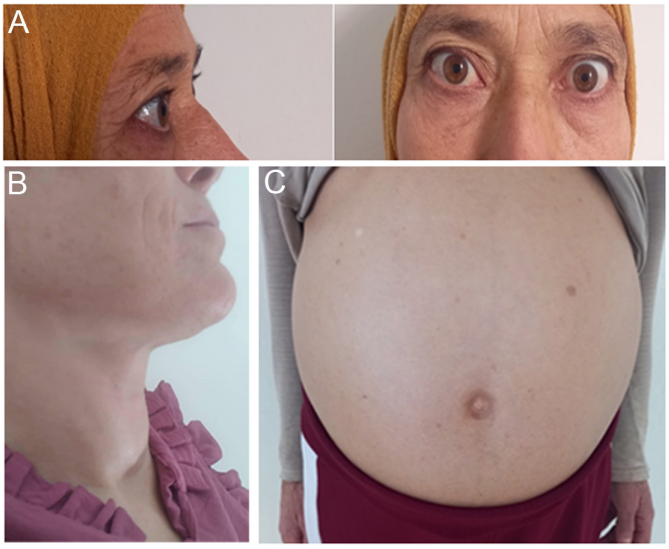

Figure 1. (A) Asymmetric bilateral exophthalmos. (B) Visible thyroid goiter. (C) Abdominal distension.

The thyroid analysis revealed hyperthyroidism [thyroxine = 12.8 ulU/mL; thyroid-stimulating hormone (TSH) = 0.008 ulU/mL].

A thoracic and abdominal computed tomography was performed and revealed cardiomegaly, circumferential pericardial effusion of low abundance, pleural effusion of medium abundance, and ascites of high abundance.

Exploratory puncture of the ascites fluid revealed a sterile exudative fluid with no evidence of Koch bacillus in the direct examination with no neoplastic cells. The transthoracic cardiac echography revealed dilated cardiomyopathy with a left ventricular ejection fraction (LVEF) of 54% and dilatated inferior vena cava and hepatic veins. Cardiac magnetic resonance imaging showed biventricular dilatation with LVEF 29%, and no ischemic necrosis or myocarditis sequelae (Figure 2A).

A neck ultrasound showed a homogeneous hypervascularized goiter; the radionuclide thyroid scanning showed a thyroid in place, with increased uniform tracer uptake (Figure 2B).

At this stage, Graves' disease was suspected. Antinuclear antibodies (ANAs) were positive at a title of 460, with positive anti-TSH receptor antibodies at 35 IU/mL and anti-thyroid peroxidase antibodies (anti-TPO) at 312 IU/mL.

Given the cardio-thyrotoxicosis, the patient received intravenous and then oral furosemide besides 30 g of thiamazole, daily with propranolol 40 mg/day.

MAIN POINTS

- Severe acute respiratory syndrome coronavirus-2-induced auto-immune diseases and particularly thyroiditis should be known by physicians.
- Grave's disease can have an unusual revealing presentation with edema and acute cardiac failure.
- Thyroid function assessment should be conducted in post-coronavirus disease 2019 unusual symptoms.

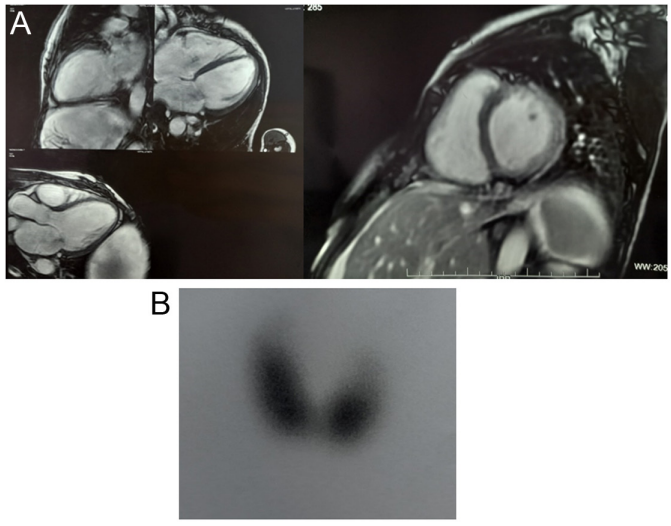

Figure 2. (A) Cardiac magnetic resonance imaging showing biventricular dilatation. (B) Tc99m scintigraphy of the thyroid showing an intense and homogeneous uptake in relationship with Graves' syndrome.

The control of ANAs showed a lower level at 1/100, and anti-DNA and anti-extractable antinuclear antigen antibodies were negative.

The patient was referred to an endocrinology department for further assessment and treatment of Graves' disease and she had an ophthalmic examination; the orbitopathy clinical activity score was 2 and it was judged suitable for iodine treatment by our colleagues: endocrinologists and ophthalmologists.

During the follow-up, clinical improvement was remarkable, and the thiamazole dose was reduced progressively until reaching euthyroidism. Six months later, the patient had radioiodine therapy. The ophthalmopathy, the goiter, and ascites regressed (Figure 3).

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

Discussion

Graves' disease is an autoimmune thyroid disorder (AITD) due to the presence of stimulating anti-TSH-receptor antibodies and is the most common explanation for hyperthyroidism. It affects mostly females and peaks in middle age.[1] Triggering an autoimmune response during COVID-19 infection may induce the onset or relapse of Graves' disease.[2] The onset of this disease after SARS-CoV-2 doesn't need a preexisting thyroid disease, which was shown in the literature.[3] Two cases of Graves' disease related to COVID-19 were reported by Mateu-Salat et al.[4] In one case, the patient had a previous history of Graves' disease in remission for 30 years which

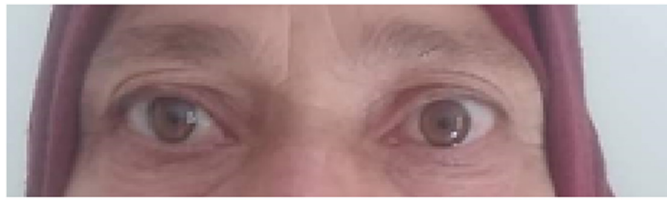

Figure 3. Evolution after treatment.

relapsed in the month following COVID-19 infection, while the other had no history of thyroid pathology.[2] The time between the onset of thyroiditis and SARS-CoV-2 infection varies widely in the literature ranging from concomitant onset to 90 days.[5] In the present case, we believe there was a diagnostic delay. In fact, the patient reported hyperthyroidism-related signs that she neglected and that were evolving more than 1 month before she went to the emergency room. Hence, the duration between SARS-CoV-2 infection and the onset of Graves' disease in this case is around 2-3 months which is in line with the literature.

Compared to controls, COVID-19 patients had latent autoimmunity mediated by a higher title of autoantibodies, such as antinuclear antibodies, rheumatoid factor, and anti-TPO antibodies.[6] These findings suggest the role of SARS-CoV-2 infection in triggering or amplifying autoimmune disorders. The molecular mechanisms responsible for the development of AITDs seem to be the same observed in severe viral infections: molecular mimicry and viral superantigens that alter the T cell repertoire add to that, increased lymphocyte apoptosis and the expansion of autoreactive lymphocytes.[7,8]

Müller et al suggest that SARS-CoV-2 has an affinity to the thyroid gland via the angiotensin-converting enzyme 2 receptors, which are known to be crucial for SARS-CoV-2 to invade human cells and are more prevalent in thyroid cells than in lung cells.[9,10] Therefore, it is necessary to assume that not only the respiratory system may be a target for coronavirus, but it might also target any organ such as the heart, the kidney, the adipose tissue, or the thyroid gland.[11] The hyperinflammatory reaction associated with SARS-CoV-2 infection can trigger an immunological cascade and therefore reactivates Graves' disease. This immune response is called "cytokine storm" and is the consequence of a dysregulated immune response against pathogens. It is caused by an intensive and rapid release of cytokines into the bloodstream from over-activated immune cells, leading to uncontrolled inflammatory responses.[12] It is interesting to point out that while the inflammatory phenomenon induced by SARS-CoV-2 seems to be mainly mediated by type 1 T helper cytokines as well as interleukin-6, the pathogenesis of Graves' disease is apparently mediated by type 2 T helper autoimmune response.[2]

Concerning treatment, in most cases, antithyroid drugs and β-blockers are prescribed to reduce the symptoms of thyrotoxicosis. Glucocorticoids should be prescribed in the case of thyroid storm, orbitopathy, precrisis, or failure to control thyrotoxicosis.[13,14] Urbanovych et al[3] reported one case of Graves' disease associated with COVID-19 occurring after a SARS-CoV-2 infection which required high-dose corticosteroids to control the thyroid storm. In the case of our patient, antithyroid drugs were sufficient to obtain euthyroidism and she then had radioactive therapy.

Conclusion

Based on the pathophysiology of SARS-CoV-2 infection and invasion of the thyroid gland and many similar case reports of post-SARS-CoV-2 infection auto-immune diseases and endocrinopathies, we suggest that clinicians should keep an eye on thyroid function in the acute phase for COVID-19 patients and during convalescence to diagnose hyperthyroidism before the onset of complications and control reversibility.

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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