


Hashimoto's thyroiditis following SARS-CoV-2 infection

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SUMMARY

Infectious diseases have long been considered one of the triggers for autoimmune and autoinflammatory diseases. Since the appearance of the new coronavirus in December 2019 in the city of Wuhan, China, there have been many reports suggesting that infection with coronavirus 2 (SARS-CoV-2) precedes the appearance of several autoimmune and autoinflammatory diseases. We describe a case report of a patient who was infected with the SARS-CoV-2 virus and later developed a picture of Hashimoto's thyroiditis.

BACKGROUND

Hashimoto's thyroiditis is an autoimmune disease, characterised by an infiltration of intrathyroidal mononuclear cells leading to the production of autoantibodies against agents present in the thyroid gland, such as thyroglobulin (Tg) and thyroid peroxidase (TOP).¹ Consequently, there is an impairment of thyroid function, causing a negative impact on the production of hormones produced by the gland, triiodothyronine (T3) and thyroxine (T4).² The diagnosis of Hashimoto's thyroiditis is currently established by a combination of clinical characteristics, whether focal, by compression caused by the possible enlargement of the gland leading to dyspnoea and dysphagia, in addition to systemic symptoms such as adynamia, constipation and drowsiness, caused by low production of thyroid hormones. In the biochemical picture, the levels of thyroid hormones, T4 and T3 are evaluated and are usually suppressed, commonly associated with an elevation of thyroid stimulating hormone (TSH).³ In addition, the presence of serum antibodies against thyroid antigens (mainly to TOP and Tg) is seen in 90% of the cases of Hashimoto's thyroiditis.⁴ As for its aetiology, a series of studies have indicated that environmental factors play a critical role in the development of Hashimoto's thyroiditis, and a growing body of evidence suggests viral infection, one of the triggering factors of the disease.⁵ In December 2019, a new type of coronavirus was discovered in Wuhan, China, bringing a panorama of global impact.⁶ The condition developed by the virus is associated with symptoms of pulmonary involvement, mainly, but gastrointestinal and rheumatoid symptoms have also been elucidated. The pathophysiology of the infection is still uncertain, but some pathologies have been associated after contact with the SARS-CoV-2 virus, mainly of an autoimmune nature.⁷ The present report describes the case of a patient, who became infected with SARS-CoV-2 and after remission of the condition,

developed Hashimoto's thyroiditis. Thus, we propose the hypothesis of a possible relationship of autoimmune diseases triggered by SARS-CoV-2.

CASE PRESENTATION

The 33-year-old female patient came from the city of Santana de Parnaíba, São Paulo. The patient was infected with SARS-CoV-2, demonstrated by real-time PCR test using a nasopharyngeal swab sample on 1 November 2020. Twenty days later, the patient sought healthcare service, reporting fatigue and severe hair loss. Laboratory tests for thyroid function were ordered, as well as thyroid ultrasound. The test results elucidated altered TSH levels of 8 mIU/mL (upper limit of the normal range of 4.3 mIU/mL); free T4 of 0.5 ng/dL (normal range 0.7–1.8 ng/dL) and antibodies, anti-Tg of 252 IU/mL and anti-TOP of 115 IU/mL (normal range less than 60 IU/mL for both). Ultrasonographic examination of the thyroid showed the presence of diffusely hypoechoic and heterogeneous glands. She was prescribed to start pharmacological management with levothyroxine sodium (Levoid) 25 µg. After 8 weeks, the patient was instructed to undergo thyroid function laboratory tests again, which showed TSH of 6.4 mIU/mL, free T4 of 0.9 ng/dL and anti-TOP reduced to 55 IU/mL; in addition to laboratory parameters, the patient reported improvement in fatigue symptoms. Management remained, but with increased dosage of Levoid to 38 µg. Eight weeks later, new laboratory tests were again collected, which showed a TSH of 2.2 mIU/mL, free T4 1.2 ng/dL, negative anti-TOP antibody and persistent improvement of clinical symptoms, elucidating the stabilisation of thyroiditis. In January 2021, the patient performed a genetic test, which assesses the genotyping of markers, observing a predisposition to exacerbation of proinflammatory cytokines, supported by polymorphisms in the tumour necrosis factor (TNF) alpha and interleukin (IL)-6 genes, where the patient's alleles can be seen in [table 1](#).

DISCUSSION

The COVID-19 pandemic, caused by SARS-CoV-2, remains a global challenge for physicians and scientists. Case reports of patients infected with coronavirus who subsequently developed autoimmune diseases are increasingly elucidated.⁷ Considered the most common endocrine disorder, a Hashimoto's thyroiditis has a very varied aetiologies, causing viruses, which are cited as the main environmental factor involved in subacute thyroiditis and autoimmune thyroid diseases.⁵ In this case, we address the correlation between the development of a



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Table 1 Description of the variants analysed in the genetic test

Risk of hyperinflammation				
Gene	Polymorphism	Patient's alleles	Comments	Reference
1. TNF	rs1799724	CT	Allele T: related to increased levels of TNF α .	Mlak <i>et al</i> ²⁰
2. TNF	rs1800693	CC	Allele C: related to the higher incidence of inflammatory diseases	De Jager <i>et al</i> ²¹
3. IL-6	rs1800795	CG	G allele: related to increased levels of IL-6	Tartert <i>et al</i> ²²
4. IL-6	rs1800796	GG	G allele: related to increased levels of IL-6	Bull <i>et al</i> ²³

Some variants are related to the increased risk of inflammation. The numbering alleles 1, 2, 3 and 4 showed higher risk of inflammation. IL, interleukin; TNF α , tumour necrosis factor alpha.

Hashimoto's thyroiditis after infection by the SARS-CoV-2 virus, due to clinical and laboratory changes in diagnosis for pathology. Thus, we propose the hypothesis of the impact of SARS-CoV-2 viral infection on the development of autoimmune pathologies, such as thyroiditis.

To assist in the diagnosis of Hashimoto's thyroiditis, ultrasonographic findings of heterogeneous goitre with diffuse hypoechogenicity are of great diagnostic importance when correlated with clinical and laboratory tests, which is compatible with the patient described in the report.⁸ The viral infection creates an environment that stimulates autoimmunity in genetically susceptible individuals.⁹ The infected cell can trigger a molecular mimicry, the virus expresses a particle similar to the host's self, stimulating an aggressive immune response to the entire tissue.⁹ The inflammatory stimulus of infection corroborates to a bystander activation, influencing the release of autoantibodies at the locus, encouraging antigen-presenting cells to epitope spreading, activating T lymphocytes, mainly CD8+.⁹

In COVID-19, due to the viral tropism in the thyroid by the presence of ACE 2, binding stimulates the release of IL-6, triggering the whole molecular mimicry.¹⁰ The patient has a high chance of subclinical thyrotoxicosis, abnormalities in the gland and the drop in T3 as a significant prognostic factor in the disease.¹⁰ The viral binding provides abnormalities characteristic of autoimmunity, even though the antibodies that act against the thyroid are negative.¹⁰

Genetic analysis of the patient revealed variations in the genes of proinflammatory cells such as TNF-alpha and IL-6 by studying her polymorphisms. Both are considered inflammatory cytokines that occur primarily in acute inflammatory processes, but if their levels remain chronically high, they may promote an increased risk of autoimmune disease.¹¹ Thus, genetic variants associated with TNF-alpha and IL-6 have been found to make cells inherently more active, predisposing to potential chronic inflammation as seen in Hashimoto's thyroiditis.¹²

A study published by Croce *et al*¹³ examined six studies aimed at assessing thyroid function in patients with COVID-19. They found low TSH and T3 levels in the infected patients, and some with normal T3 and T4 levels. To understand the mechanism of damage to the gland, they compared the involvement of other coronaviruses such as SARS-CoV-2.¹³ Autopsy patients showed changes in the structure and morphology of the epithelial cells of the glandular follicle, in addition to a decrease in TSH-producing cells in the pituitary gland, demonstrating the concomitant involvement of the hypothalamic-pituitary-adrenal axis. In the same context, a cohort study conducted in Seoul city in 2021 by Lui *et al*¹⁴ followed 122 patients to check the presentation of thyroid autoimmunity after COVID-19. An increase in anti-TOP and anti-Tg was observed 3 months after acute viral infection, which is similar to other presentations of viral infections such as T-lymphotropic virus type I.¹⁴

The pathogenesis of Hashimoto's thyroiditis is an important subject of investigation because it has not been fully elucidated.

However, studies suggest that a possible trigger may be dysfunction of CD4 + CD25+ differentiating regulatory T cells (Tregs),¹⁵ since Hashimoto's thyroiditis involves an autoimmune response mediated by autoreactive T cells, which is induced by an alteration in Tregs signalling.¹⁶ Tregs are identified by the expression of the transcription factor Forkhead Box P3 (FOXP3),¹⁷ suggesting that it is in the context of abnormal expression of FOXP3 that the autoimmune process in question may be triggered. FOXP3 is negatively regulated by SIRT1, a nicotinamide adenine dinucleotide-dependent protein deacetylase.¹⁸ In an inflammatory process, there is a serum increase in circulating proinflammatory ILs, which promotes an increased oxidative stress scenario, leading to impaired signalling in the SIRT1 pathway.¹⁹ We question the possible pathophysiology of Hashimoto's thyroiditis and SARS-CoV-2, which is supported by the hypothesis that oxidative stress from COVID-19 infection causes an alteration in the sirtuin signalling pathway and consequently an altered expression of FOXP3, which favours the milieu for the activation of autoimmunity, such as Hashimoto's thyroiditis.

Learning points

- ▶ To describe the case of a patient who developed Hashimoto's thyroiditis after COVID-19 infection and was treated pharmacologically with levothyroxine, with a good clinical response.
- ▶ To describe the possible influence of genetic polymorphisms in proinflammatory genes, favouring chronic inflammatory signalling and the trigger for autoimmune diseases.
- ▶ To describe the possible pathophysiology of Hashimoto's thyroiditis after SARS-CoV-2 infection, caused by an alteration in the sirtuin pathway, favouring the activation of autoimmune conditions.

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