doi: 10.4183/aeb.2023.471

MANAGEMENT OF THYROIDITIS IN THE CONTEXT OF COVID-19: CAUSE-EFFECT AND BEYOND

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Abstract

Background. The COVID-19 pandemic hit the world in late 2019, and by 2020, everyone was affected. Severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) belongs to the beta-coronavirus genre and uses the angiotensin-converting enzyme 2 (ACE2) receptor to penetrate cells. Thyroid cells are rich in such receptors. Therefore, this gland is frequently involved alongside other organs in the COVID-19 disease.

Aim. To describe COVID-19 inflammation and, eventually, dysregulations of normal thyroid function in a case series of patients diagnosed in a tertiary endocrinology care centre.

Patients and Methods. We described subacute thyroiditis cases related to COVID-19 infection or vaccination against SARS-CoV2 infection (clinical manifestations and evolution). We also reviewed the literature data regarding COVID-19 infection or vaccination implications in thyroid pathology.

Results. The literature describes two types of thyroid involvement in SARS-CoV2 infection or vaccination: subacute thyroiditis (SAT) and non-thyroidal illness syndrome (NTIS). In our case series, 5 patients (3 males), aged 41-54 years, developed the classical clinical manifestation of SAT related to COVID-19 infection (3 patients, concomitantly to upper respiratory infection or a few weeks apart) or anti-SARS-CoV2 ARNm vaccination (1-2 weeks after the vaccine administration). Clinical, laboratory and imaging findings and the evolution (steroid anti-inflammatory treatment used in 4/5 cases) were unremarkable compared to other SAT etiologies.

Conclusion. We found no differences between the "typical" viral and post-COVID-19 SAT regarding clinical presentation, severity, response to treatment, and thyroid function alteration. The only remarkable difference is the association of SAT with anti-SARS-CoV2 ARNm vaccination.

Keywords: COVID-19, subacute thyroiditis, non-thyroidal illness, SARS-CoV-2, vaccine.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the beta-coronavirus genre and is an enveloped RNA single-strand positive sense virus. The Coronaviridae Study Group recognises this virus as forming a sister clade to the prototype human and bat severe acute respiratory syndrome coronaviruses (SARS-CoVs) of the species severe acute respiratory syndrome-related coronavirus and designates it as SARS-CoV-2 (1). It is already widely known that the receptor to which SARS-CoV-2 binds before releasing the viral riboprotein complex into the host cell is angiotensin-converting enzyme 2 (ACE2) (2), which is present in the epithelial multiciliate cells in the nasopharynx or trachea, or support cells in the nasal olfactory mucosa and not only (3). Endocrine organs have cells expressing ACE2, the higher concentration being found in the testis, followed by the thyroid. The virus can invade the pancreas, ovary, adrenal gland, pituitary gland, and hypothalamus cells as they have ACE2 on their surfaces (4-6). After entering the host cells, SARS-CoV-2 induces direct cytopathic reactions by affecting cellular organelles (mitochondria, endoplasmic reticulum, nucleus or Golgi Apparatus) (7). In the meantime, the innate immune system is activated and will produce antiviral cytokines and chemokines (8). Pathogen-associated molecular patterns and damage-associated molecular patterns are activated and lead to the production and elimination of different molecules that are intended to enhance antiviral activity (9).

Severe forms of COVID-19 result from a combination of direct damage induced by SARS-CoV-2 and an abnormal host immune-inflammatory response. As initially supposed to be based on the evolution of the disease and then proved by different inflammatory

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markers, dosing these severe forms results from an exaggerated immune-inflammatory response (9). In our experience, dosing CRP and IL-6 was extremely relevant for identifying patients developing severe forms of COVID-19. Oxidative stress may also be important in the pathogenesis of severe COVID-19 forms (10).

Immunosuppression, on the other hand, can also play a role in the severe COVID-19. Lymphopenia is frequently encountered in patients with COVID-19, and its severity correlates with the disease severity and even mortality (11). Lymphopenia may be involved in at least two modes: first, clearance of the virus is deficient, and therefore, these patients may have higher viral loads and be more and longer contagious; second, bacterial infections may be easier acquired in lymphopenic patients.

Clinical manifestations

The incubation period is about 4-5 days, with a maximum of 14 days after exposure. With the latest variants of SARS-CoV-2, the incubation period might be even shorter, of 2-3 days (12). The disease can be completely asymptomatic, mild to moderate or severe. With time and the change of strains of SARS-CoV-2, clinical manifestations have changed. For example, at the beginning of the pandemic, smell and taste alterations were more frequent initially, while now the most frequently encountered manifestations are cough, fever, myalgias and headache (13, 14). In addition, dermatological, cardiovascular, gastrointestinal, neurological and haematological complications are relevant. Thyroid involvement is frequently asymptomatic during the COVID-19 disease but may sometimes manifest with neck pain/tenderness and tachycardia.

SARS-CoV-2 and thyroid – general concepts

The thyroid expresses the ACE2 receptor, thus being a possible target for SARS-CoV-2. The Thyroid produces Thyroxine (T4), a prohormone and the active triiodothyronine (T3), with effects on every nucleated cell of all tissues; they also contribute to the modulation of the immune system (15). Their activity influences cell-mediated immunity, the proliferation of T and B lymphocytes, and the activity of the natural killer cells and interferons (15, 16). Although patients with poorly controlled thyroid diseases do not have a greater risk of contracting viral infections, they definitely have a higher risk of developing more severe forms of the disease and complications (17).

The relationship between COVID-19 and the thyroid is bivalent: the effects of thyroid dysfunction (hypothyroidism and hyperthyroidism) on the evolution of the viral disease and the effects of COVID-19 on the thyroid function, focusing upon subacute thyroiditis after viral infection. In the following we will analyse this relationship.

Thyroid dysfunction after COVID-19 vaccination

WHO has approved COVID-19 vaccines for their safety and efficacy; they can offer protection against SARS-CoV-2 infection. However, they have been associated with very rare complications, such as autoimmune thyroid disorders. Among 83 reported cases in one review, most thyroid dysfunctions were observed after vaccinations with mRNA-based vaccines (68.7%), followed by viral vector vaccines (15.7%) and 14.5% cases following inactivated vaccines. Subacute thyroiditis was the most common COVID-19 vaccination-related affection (60.2%) followed by Graves'disease (25.3%) (18). Other forms of thyroid disease have been described: focal painful thyroiditis, overt hypothyroidism, painless thyroiditis with thyrotoxic periodic paralysis. Silent forms of thyroiditis have also been described. The onset of the symptoms occurred following the first vaccine dose, with a median of 10.0 days after vaccination. Fewer patients developed thyroiditis after the second dose of the vaccine (18).

Most cases that appeared after the inactivated vaccine have been caused by adjuvants, triggering adverse reactions in genetically predisposed subjects. In a case report of subacute thyroiditis postvaccination from Germany, symptoms were attributed to the adenovirus vector and mRNA vaccines (19).

The mechanism of postvaccination-associated thyroid disorders remains unknown in detail. One hypothesis is that the vaccine may produce an immune response that triggers thyroid autoimmune inflammation in at-risk patients. Another hypothesis is that the spike protein of SARS-CoV-2, nucleoprotein, and membrane proteins cross-react with thyroid peroxidase (20).

COVID-19 vaccine-induced thyroiditis can manifest in silent or subacute forms. It is more frequently encountered in women than in men but is a rare manifestation. Clinicians should consider this possible diagnosis when investigating thyroid dysfunction, especially if the patient has had a COVID-19 vaccine before the episode (21).

Our experience – cases of SAT.

Case 1

A 47-year-old woman presented to our clinic for the first time in early March 2021. The onset of symptoms was a month before, about two weeks after vaccination with mRNA-based COVID-19 vaccine against SARS-CoV-2: she presented with polymorphic symptomatology, including myalgia, asthenia, and intermittent low-grade fever episodes, which did not improve under anti-inflammatory therapy with Ibuprofen 800 mg/day for nine days. At the initial outpatient evaluation, the patient presented without any other symptoms suggestive of a recent upper respiratory tract infection; the biological tests revealed a progressively increasing inflammatory syndrome without leukocytosis with altered thyroid function (low TSH, high freeT4), for which she had been treated with Thiamazole (20 mg/day) 4 days before presenting to the hospital.

In the endocrinology department, the patient had a WHO grade I goitre, mildly tender to palpation, especially in the right lobe, and thyroid hormone levels showed a suppressed TSH, with FT4 and T3 within normal limits and normal thyroid antibodies. Ultrasound of the anterior cervical region revealed: a heterogeneous structure in the right lobe, with a hypoechoic area (16/59 mm) and increased vascularity; the left lobe presented an intensely heterogeneous, hypoechoic, diffuse pseudo-nodular structure with increased vascularity.

Based on clinical, laboratory, and imaging findings (Table 1), a diagnosis of subacute thyroiditis was made, and oral corticosteroid therapy was initiated with methylprednisolone 32 mg/day (0.5 mg/Kg/day).

The symptoms improved in a few days, and about three weeks after the initiation of corticosteroid therapy, markers of inflammation normalized, and thyroid function returned to normal. Therefore, a gradual tapering of glucocorticoid doses was decided, decreasing by 4 mg every 4 days until discontinuation. At the same time, it was decided to start levothyroxine replacement therapy (25 µg/day), given that FT4 was at the lower end of the normal range and TSH was rising (Table 2).

On the ultrasound evaluation performed 5 months after diagnosis, the thyroid showed normal size and structure, with normal vascularity. Thyroid function remained within normal limits, leading to the decision to discontinue levothyroxine replacement therapy. The patient maintained her euthyroid state even one year after stopping the treatment.

Case 2

A 41-year-old male patient with no significant medical history presented to the endocrinology department in October 2020, complaining of sore throat, difficulty swallowing solid food, mild cough, weight loss (10 kilograms in one month), tremors in the extremities, lack of appetite and an altered general condition progressively accentuated in the last several weeks.

On the general practitioner's recommendation, the patient underwent laboratory tests, which showed a mild leukocytosis with neutrophilia and an inflammatory reaction with increased levels of fibrinogen, ESR and CRP. In addition, hyperthyroidism was suggested by TSH levels (0.004) and FT4 levels (2.62 ng/dl, normal range 0.7-1.48 ng/dl). At the initial outpatient evaluation, the patient tested negative against SARS-CoV-2 (IgM, IgG antibodies). A treatment plan had been started five days before the admission to our clinic, with symptomatic therapy, antibiotic therapy with clarithromycin and thiamazole 30 mg/day, but no obvious improvement in his condition was observed.

At presentation, the patient was of normal weight, in a febrile episode (38.4 degrees Celsius) and had clinical signs suggestive of thyrotoxicosis, such as tachycardia (heart rate of 112 beats per minute), extremities tremors and hyperemic moist skin. Palpation of the anterior cervical area revealed a small, firm, sensible goitre. Laboratory data revealed leukopenia, inflammatory syndrome and hyperthyroidism (TSH=0.0051 uIU/ml (0.5-4.5), FT4=30.12 pmol/l (9-19)) with negative autoimmune markers (ATPO and TRAb negative) (Table 1). An inhomogeneous hypoechogenic structure with bilaterally increased vascularity was observed on thyroid ultrasound. A diagnosis of subacute thyroiditis was established, leading to the initiation of glucocorticoid therapy (methylprednisolone - 24 mg/day = 0.3 mg/Kg/Day).

The outcome was favourable, with a significant improvement in symptoms after glucocorticoids: a reduction in previous cervical pain and an improvement in dysphagia, all without recurrence of febrile episodes. Two days after admission, the SARS-CoV-2 PCR test returned positive, which led to the transfer of the patient to a hospital specialized in the care of patients with COVID-19. The recommendation was to continue glucocorticoid therapy with a gradual dose reduction and to reassess thyroid function after one month; however, the patient did not present for the scheduled reevaluation.

Case 3

A 54-year man with previous known thyroid pathology (multinodular goitre, subacute thyroiditis 16 years ago) was admitted in October 2021 for anterior

cervical pain, dysphagia, dysphonia, and weight loss (6 kilos in one month), associated with significant inflammatory syndrome and thyrotoxicosis in laboratory explorations done in the outpatient setting. One week before the onset of symptoms, the patient received the mRNA COVID-19 vaccine.

On examination, the patient was of normal weight, with normal cardiological findings, normal skin, a thyroid gland with moderately increased dimensions, firm consistency, heterogeneous texture, tenderness to palpation, and normal movement with swallowing.

The evaluation in our clinic confirmed thyrotoxicosis with elevated freeT4 (30.21 pmol/l, NV=9-19)) and T3=263.71 ng/dl (NV = 50-200 ng/dl) levels and suppressed TSH levels (0.0026 mUI/L(NV=0.5-4.5)), as well as incomplete inflammatory syndrome – mild thrombocytosis, no leucocytosis, high ESR, CRP and fibrinogen (table 1). Corticosteroid therapy was initiated (prednisone at 30 mg/day, 0.4 mg/kg/day) with gradual dose reduction (5 mg every week), with rapid improvement of symptomatology, but the patient was lost to follow-up (Table 2).

Case 4

A 41-year-old male patient with signs and symptoms suggesting subacute thyroiditis, which began approximately 2 weeks before evaluation (pain in the anterior cervical region, odynophagia, approximately 5 kg weight loss in 2 weeks, sweating), not relieved by NSAIDs and paracetamol administration, was admitted to our clinic in December 2021.

On clinical examination, the patient was of normal weight, mildly tachycardic, with a thyroid gland of normal dimensions, elastic consistency, heterogeneous texture, sensitive to palpation and movable with swallowing.

The biological evaluation showed increased fibrinogen, ESR, and CRP without affecting the leukocyte count, with values of the pituitary-thyroid axis suggestive of thyrotoxicosis: TSH=0.0043 mUI/L (NV=0.5-4.5), FT4=38.36 pmol/l (NV=9-19), T3=355.47 ng/dl (NV=50-200 ng/dl) (table 1).

On ultrasound examination, the thyroid had a slightly increased volume and a heterogeneous structure, with a poorly defined hypoechoic area of approximately 20 mm with peripheral weak vascularity in the lower 2/3 of the right lobe and a similar 12 mm area with mild peripheral increased vascularity in the upper 1/3 of the left lobe.

Additionally, blood tests indicated a high titer of Anti-SARS-CoV2 IgG antibodies (42.5 IU/ml, ≥ 15 IU/ml—positive), but the patient was unable to recall any significant recent episodes of upper tract infection suggestive of COVID-19, and he had not received the SARS-CoV-2 vaccine. Thyroid antibodies were normal, as well as rapid tests for other upper respiratory tract infections (Adenovirus, Coxsackie).

Corticosteroid therapy was initiated: Methylprednisolone 25 mg/day, 0.4 mg/kg/day for 2 weeks, with a gradual (4 mg/week) tapering of the dose; with rapid improvement of symptoms; however, the patient was lost to follow-up.

Case 5

A 46-year-old female patient was admitted to our clinic in February 2021 for anterior neck pain radiating to the ear and odynophagia, which began approximately 4 weeks after testing positive for SARS-CoV-2, despite being asymptomatic (without suggestive symptoms of SARS-CoV-2 infection). Biological tests confirmed incomplete inflammatory syndrome with high ESR (33 mm/h), high fibrinogen (589 mg/dl, NV = 170-350) and high CRP (4.3 mg dl, NV = 0-0.5); the hormonal evaluation demonstrated suppressed TSH levels (0.005 mUI/L) with elevated values of thyroid hormones (fT4 = 36.5 pmol/l, NV = 12-22 pmol/l). Thyroid ultrasound showed symmetric subacute inflammatory involvement affecting both lobes (mild increase in thyroid volume, heterogeneous, pseudonodular) (Table 1).

She received non-steroidal anti-inflammatory therapy with NSAID (etoricoxib) and beta-blockers, with symptom improvement in about 1 week and normalising inflammatory markers in about 7 weeks. Thyroid function evaluation at 7 weeks from diagnosis revealed thyroid hypofunction, with slightly elevated TSH levels (8.82 mUI/L) and reduced free T4 levels (6.11 pmol/l, NV = 12-22) (Table 2). Substitutive therapy with levothyroxine (37.5 mcg/day) was initiated, maintaining normal TSH levels during a follow-up period of 15 months. Later, the patient did not return for further assessment, so potential normalization of thyroid function could not be documented.

DISCUSSION

Effects of thyroid dysfunction on the evolution of COVID-19

Hypothyroidism

As mentioned above, patients with hypothyroidism have a lower level of immunity, but overall, no increased risk of developing COVID-19 or even hospitalisation or complications has been found in more studies (21, 22). The rate of hypothyroidism

Table 1. Clinical and laboratory findings at the time of diagnosis

No	Age/ Sex	Context	Time* (weeks)	ARN SARS-CoV2	Ab against SARS-CoV2	Clinical	Biological profile before treatment			Hormonal profile			Cervical Ultrasound	
							ESR	RCP	Fibrinogen	TSH	fT4*	T3 /fT3***	Pattern	Lateralization
1	47y/F	V	2 weeks after the vaccination	negative	NA	Anterior cervical pain myalgia, asthenia, low-grade fever	60	41.4	472 667	<0.015	1.1	NA	heterogeneous, hypoechoic, diffuse pseudo-nodular structure with increased vascularity	LL>RL
2	41 y/M	URTI	Concomitant with Upper respiratory tract infection symptoms	**positive**	NA	Sore throat, mild cough, weight loss (10 kg/1 month), lack of appetite, altered general condition, fever, tachycardia	89.7	1.1	491.7	0.051	1.58	NA	an inhomogeneous hypoechogenic structure with bilaterally increased vascularity	No
3	54 y /M	V	One week after the Vaccination	negative	NA	Anterior cervical pain, dysphagia, dysphonia weight Loss (6 kg/1 months)	84.2	4.94	972	0.0026	1.59	1.32	NA	No
4	41y /M	No URTI	?	negative	**42.5IU/ ml**	Anterior cervical pain, dysphagia, weight loss (5 kilo/2 weeks)	82.2	5.64	941	0.0043	2.01	1.77	Inhomogeneous, with hypoechoic areas in both lobes, low and increased vascularity	No
5	46y/F	URTI	6 weeks	NA	NA	Anterior cervical pain, irradiated to the ear, odynophagia	39	4.3	589 (1.68 ULN)	0.005	1.66	1.7	Heterogeneous, pseudo nodular	No

V – vaccination, URTI – Upper respiratory tract infection. Time* - the time lap between vaccination/ infectious disease and SAT (expressed in weeks)
ESR = 1-30 mm/h. RCP = 0.1-0.5 mg/l. TSH laboratory normal values =0.5-4.5 µUI/ml. Fibrinogen laboratory normal values = 200-400 mg/dl. ULN – upper limit of normal. *Values are expressed as reported to the ULN. NA – not available.

in the COVID-19 population was similar to the rate of hypothyroidism in the general population, concluding that hypothyroidism is not a risk factor for COVID-19 (23, 24).

Hyperthyroidism

Hyperthyroidism is associated with an exaggerated response of the immune system. Therefore, it would be plausible that patients with uncontrolled hyperthyroidism are more prone to develop severe COVID-19 and complications of the disease. One study suggests that patients with hyperthyroidism are indeed at risk of developing complications and staying in the hospital longer than those with normal thyroid function (25). The risk of contracting COVID is not increased in patients with higher levels of thyroid hormones. Still, medication for hyperthyroidism can influence this risk: anti-thyroid medication may lead to agranulocytosis, and glucocorticoids used, for example, in Graves ophthalmopathy, can also lead to immune suppression.

Effects of COVID-19 on thyroid

Two types of thyroid involvement have been described: subacute thyroiditis (SAT) and non-thyroidal illness syndrome (NTIS).

Subacute thyroiditis

Subacute thyroiditis represents a self-limited inflammatory disorder of the thyroid that usually resolves by itself in a few months, characterised by signs of thyrotoxicosis, painful goitre without inflammatory signs of the cervical skin and fever. It is also called painful subacute thyroiditis or nonsuppurative thyroiditis, and the main cause is considered to be a viral infection. In many patients, subacute thyroiditis is preceded by an upper respiratory tract infection, and a clear relationship with Coxsackievirus, mumps, measles, adenovirus, Dengue and SARS-CoV-2 has been established (26). Thyroid autoimmunity does not seem to be involved, but a strong correlation with several types of human leukocyte antigen haplotypes (HLA-B*18:01, HLA-DRB1*01, or HLA-C*04:01, HLA-B*35) has been described in many ethnic groups (27).

The inflammation leads to the rupture of the follicles and the release of the reserve hormones in the circulation, with consecutive clinical and biochemical thyrotoxicosis. This state lasts until the stores of thyroglobulin are exhausted because new hormone synthesis also ceases, not only because of damage to the thyroid follicular cells but also because the increased serum T4 and T3 concentrations inhibit thyroid-stimulating hormone (TSH) secretion. Some patients with subacute thyroiditis may also experience hypothyroidism in the second part of the disease before re-entering euthyroidism.

The clinical manifestations of subacute thyroiditis may appear suddenly or gradually and are often preceded by upper respiratory tract manifestations. The clinical picture is dominated by pain, which is almost always present. The pain may be limited to the thyroid area or irradiate to the upper neck, jaw, throat, upper chest, or ears. Fever, fatigue, malaise, anorexia, and myalgia are common (28). The thyroid gland is typically slightly or moderately diffusely or asymmetrically enlarged and nearly always tender. Both thyroid lobes are involved from the beginning in most patients. Still, the pain, tenderness, and enlargement can be unilateral or start on one side and later spread to the other side for days or even weeks (so-called "creeping thyroiditis") (24). At the beginning of the clinical manifestations, approximately one-half of patients have symptoms and signs of thyrotoxicosis (palpitation, fatigue, insomnia).

Table 2. Treatment and follow-up

No	Age (y)/Sex	Treatment Type of treatment	Corticotherapy Initial dose	Time of treatment	Biological resolution	Hypothyroidism on follow-up (Yes/NO)	Recurrence (Yes/NO)
1	47/F	Thiamazole 4 days, then **Methylprednisolone**	32 mg/d (0.5 mg/kg/day)	5 weeks	Yes, in 3 weeks	Yes, in 5 weeks, for 5 months	No
2	41/M	Clarithromycin, thiamazole for 5 days, then **Methylprednisolone**	24 mg/d (0.33 mg/kg/day)	NA	NA	NA	NA
3	54/M	**Prednisone**	30 mg/d (0.4 mg/kg/day)	NA	NA	NA	NA
4	41/M	**Methylprednisolone**	24 mg/d (0.4 mg/kg/day)	NA	NA	NA	NA
5	46/F	NSAIDs, propranolol	No	7 weeks	Yes, in 7 weeks	Yes, at 7 weeks, for at least 15 months	No

NSAIDs – non-steroidal anti-inflammatory drugs.

The typical biological findings are increased inflammatory markers (erythrocyte sedimentation rate, circulating C-reactive protein (CRP) concentration and plasmatic fibrinogen concentration) with usually normal neutrophil and lymphocyte count. The thyroid function may evolve in three phases: the first one, thyrotoxic, characterised by suppressed TSH and normal, high normal or even high serum levels of fT3 and fT4; a second hypothyroid phase (not necessarily in all cases), following destruction of the thyroid follicles, identified by high TSH with normal or low normal fT3 and fT4, and the third-the recovered euthyroid phase.

The typical ultrasound pattern is an intense hypoechoic, heterogeneous, pseudo-nodular thyroid gland with areas of high Doppler signal at the periphery of large non-vascularised areas.

In May 2020, an Italian case report provided the first case of subacute thyroiditis potentially associated with a prior mild COVID-19 infection (28). It was an 18-year-old female who developed neck pain, fever and palpitation about two weeks after a positive test for SARS-CoV-2. She had an enlarged and tender thyroid, and her blood tests were suggestively modified for subacute thyroiditis, with elevated fT3 and fT4, undetectable TSH and elevated CRP and ESR. After this first case, other cases and case series have been reported (29-31). It is important to mention that there are also cases related to COVID-19 vaccination. More than 30 articles reporting this association were published more frequently in women (32).

The treatment of subacute thyroiditis frequently involves the use of corticosteroids (33). Small initial doses of steroids combined with an extended tapering period should keep recurrence rates low. Intrathyroidal steroid injections could be a better alternative to oral prednisone, providing better safety and a more rapid onset of the action (33). Systemic use of corticosteroids poses a risk of developing adrenal insufficiency or glucocorticoid withdrawal syndrome if the duration of therapy is longer than 3-4 weeks and if a dose greater than daily hydrocortisone equivalent of 15-25 mg is used (34). After stopping glucocorticoids, ACTH stimulation of the adrenal cortex should be re-established. In most cases, the adrenal cortex will recover and produce the required cortisol levels. Time to full biochemical and clinical restitution of the hypothalamic-pituitary-adrenal axis is highly variable. After a long treatment with corticosteroids, when on a supraphysiologic dose, a more rapid tapper should be implemented, while in the case of a physiologic dose, a slower tapering approach should be used (34). Tapering is not recommended in therapies under 3-4 weeks (34).

Non-thyroidal illness syndrome

The most typical finding for NTIS is a low level of T3, with no increase in TSH. An increase in reverse T3 may also be found, but its levels can also be normal or even low in some NTIS patients (35). Low levels of T4 and also TSH may be found in critically ill patients with previous normal thyroid function (35). Reduced levels of T3 have been noted in patients with severe illnesses or after a long period of starvation and even in AIDS patients (36). The first cases of NTIS in COVID-19 patients have been described in 2021 (37). The association between NTIS and sepsis, multiple organ failure, acute kidney injury and acute liver failure has been described (38).

Pro-inflammatory cytokines like IL-6 and IL-1beta are probably involved in the pathogenesis of this syndrome (38). Increased levels of endogenous or exogenous corticosteroids and certain drugs also play a role. Severe illness impacts the entire hypothalamus-pituitary-thyroid (HPT) axis and the thyroid (39). Consistent data in the literature indicates that low serum fT3 and NTIS at admission strongly predict poor outcomes in COVID-19 patients. Serum levels of fT3 and TSH were significantly diminished in deceased patients compared to those who survived (39, 40). fT3 decrease, even if it remains within the normal ranges, is an important predictor for a severe evolution. Schwarz et al. (2021) divided a small cohort of COVID-19 patients into fT3 tertiles and observed that the bottom tertile (that included patients below the normal range and in the lower part of the normal range) had a mortality rate 6-times higher than the two greater tertiles (39). NTIS is a transient condition, with the levels of the thyroid hormones returning to normal soon after the resolution of COVID-19 (41).

We presented 5 cases (3 males) of SAT in the context of COVID-19 infection / specific vaccination with mRNA vaccine.

In the 2 cases linked to SARS-CoV2 vaccination, SAT symptoms appeared 7-14 days after vaccination with mRNA virus.

In the 3 cases of SARS-CoV2 infection, the symptomatology of primary viral involvement was variable: in 1 case the patient was asymptomatic, with the onset of SAT symptoms occurring 4 weeks after the incidental positive testing of SARS-CoV2 infection; in 1 case, the symptomatology of respiratory tract infection overlapped with that of thyroiditis, clinically noisy (fever 39.2°C, altered general condition, odynophagia,

anterior neck pain); in the last case, the only etiological link between SAT and COVID-19 virus was the positivity of anti-SARS-CoV2 antibodies concomitant with no vaccination history and the absence of other viral etiological evidence.

Morphologically, the thyroid gland was moderately enlarged and tender, with an ultrasound description of a heterogeneous, hypoechoic pattern with variable vascularity in all cases.

Symptom improvement required corticosteroid therapy (prednisone or methylprednisolone 0.33-0.5 mg/Kg/d) in 4/5 cases, with clinical resolution described under nonsteroidal anti-inflammatory therapy in only one case. The clinical improvement was noticed in a few days, normalization of inflammatory markers requiring 3-7 weeks of therapy.

Two cases were monitored long-term, both developing hypothyroidism after the period of thyrotoxicosis, 5-7 weeks apart from the onset of symptomatology. One case returned to euthyroid status in 5 months, while the other case showed persistent subclinical hypothyroidism after 15 months of follow-up.

We found no significant differences between the ”typical” viral and post-COVID-19 SAT regarding clinical presentation, severity, response to treatment and thyroid function alteration on follow-up, also described in the literature (42). The only remarkable difference is the association of SAT with anti-SARS-CoV2 ARNm vaccination.

In conclusion, our experience thus indicates that Covid-19-induced SAT has the same clinical presentation as the ”classical” viral SAT: cervical pain, odyno/dysphagia, mild-moderate signs of thyrotoxicosis (weight loss, palpitations), and occasionally fever. Inflammatory markers were high (ESR, CRP, and fibrinogen), and thyroid function tests were suggestive of destructive thyroiditis in all cases.

Conflict of interest

The authors declare that they have no conflict of interest.

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