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IS SUBACUTE THYROIDITIS A COMPLICATION OF SARS-COV-2 INFECTION?

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Abstract: *Subacute thyroiditis (SAT) is an inflammatory condition affecting the thyroid gland, usually triggered by a viral infection or occurring after a viral illness. It is characterized by neck tenderness, along with the typical symptoms of thyrotoxicosis and an elevated erythrocyte sedimentation rate. SAT has been identified as a potential complication associated with SARS-CoV-2 infection. The aim of this study is to present and discuss two cases of subacute thyroiditis that occurred following a viral infection, potentially linked to SARS-CoV-2 infection. We describe the clinical, biochemical, and imaging features of two cases of SAT that manifested six weeks after the onset of COVID-19-associated symptoms. Both cases involved female patients, aged 58 and 39, who developed subacute thyroiditis, characterized by neck pain, fever, and fatigue. These symptoms emerged three weeks after recovering from a viral episode marked by acute coryza, cough, and anosmia. Due to a persistent fever lasting three weeks, one of the patients required hospitalization to rule out other infectious causes of prolonged febrile syndrome. Laboratory analyses revealed elevated inflammatory markers, positive serology for SARS-CoV-2 infection, thyroid function tests showed thyroid over-activity and thyroid ultrasound confirmed the diagnosis of SAT. The patients received corticosteroid treatments and beta-blockers, resulting in the complete resolution of symptoms and normalization of inflammatory markers, within three weeks after the SAT diagnosis. Post-COVID-19 thyroiditis can emerge as a potential complication of SARS-CoV-2 infection. It is crucial for clinicians to be aware of this possibility, highlighting the importance of considering post-COVID-19 thyroiditis in patients presenting with relevant symptoms.*

Key words: *subacute thyroiditis, COVID-19, SARS-Cov-2 infection, case report*

1. Introduction

The COVID-19 pandemic took the whole of humanity by surprise, presenting significant challenges for authorities, medical professionals, and the general population. Alongside the well-known manifestations of bilateral pneumonia and acute respiratory distress syndrome (ARDS) associated with SARS-CoV-2

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infection, [1] COVID-19 can also give rise to complications affecting various body systems. These complications include the cardiovascular system (such as pericarditis, myocarditis, endocarditis, vasculitis, and thromboembolic complications) [2], the digestive system (including the gastrointestinal tract, pancreas, and liver) [3], as well as the kidneys, peripheral and central nervous system, and others. Until now, it has been established that COVID-19 is a condition that can cause damage to multiple organs.

Consequently, there is a growing assumption that the SARS-CoV-2 virus may also have a detrimental effect on the thyroid gland [4], [5]. The understanding of the connection between COVID-19 and the thyroid has been continuously advancing, with an increasing influx of data on this relationship since March 2020. The thyroid gland and the virus infection along with its associated inflammatory -immune responses are known to be engaged in complex interplay [6]. Currently, the impact of acute COVID-19 on thyroid function in individuals without pre-existing thyroid disease remains to be fully clarified. Reports regarding this matter have presented conflicting findings, with observations ranging between thyrotoxicosis, euthyroidism and suppression of thyroid function. [7], [8] The thyroid gland, an essential endocrine gland in the body, plays a crucial role in regulating various metabolic functions.

Subacute thyroiditis (SAT) is a type of non-suppurative inflammation of the thyroid gland. It is characterized by symptoms like fever, and pain in the front of the neck, accompanied by classic symptoms of thyrotoxicosis preceded by an upper respiratory tract infection [9]. In the context of COVID-19, it is important to recognize SAT as a potential complication associated with the SARS-CoV-2 virus in order to prevent possible negative consequences on the body [5], [6], [10]. Healthcare professionals should consider SAT as a possibility if patients with a previous medical history of COVID-19 present with neck pain and new onset of thyroid function alterations. This consideration applies regardless of whether the patient's previous medical history indicated thyroid issues or if there is a family history of thyroid problem.

2. Objectives

The aim of this study is to present and discuss two cases of subacute thyroiditis that occurred following a viral infection, potentially linked to SARS-CoV-2 infection. The objective is to raise awareness among physicians about the importance of monitoring thyroid function in patients recovering from COVID-19.

3. Material and Methods

We describe the clinical, biochemical, and imaging features of two cases of subacute thyroiditis that manifested six weeks after the onset of COVID-19-associated symptoms.

3.1. Case presentation

3.1.1. Case 1

The female patient, aged 58, without comorbidities, vaccinated for COVID-19 in 2021, presented herself at the emergency room of the Clinical Hospital of

Pneumology and Infectious Diseases of Brasov in September 2022. She sought medical attention due to a persistent fever with an onset of three weeks, accompanied by symptoms such as headache and asthenia. Six weeks prior to experiencing these symptoms, the patient presented respiratory symptoms affecting the upper respiratory tract, including mild fever, dry cough, dysphagia, headache, and anosmia, with complete resolution after a 5-day course of oral supportive therapy without seeking medical advice. Three weeks later she developed fevers, chills, and diaphoresis. Additionally, she reported an unintentional weight loss of three kilograms, fatigue, headaches, and palpitations. Following recommendations from her primary care physician, the patient undergoes laboratory tests, which reveal the presence of anaemia and thrombocytosis. As a result, she is referred to a haematologist for additional investigations. However, due to the persistent fever, the patient decides to seek assistance from the infectious diseases service. The physician at the service decides to admit her to the hospital for further investigations aimed at determining the underlying cause of the prolonged febrile syndrome. On admission, the patient presents with a fever (38.5°C), pale, warm, and sweaty skin, normally colored pharynx, anterior neck region painful, later cervical adenopathy, normal lung sounds, tachycardia (AV= 110/min), BP-120/60 mmHg, conscious, oriented. Laboratory tests conducted upon admission revealed a white blood count of 10.76 × 10^3/L, hemoglobin of 9,6 mg/dl, and a platelet count of 636 × 10^3/L. Renal and hepatic function appear unremarkable. Inflammatory markers elevated, with an erythrocyte sedimentation rate of 120 mm/h (normal range:0–15 mm/h) and a C-reactive protein of 130 mg/L (normal range:0–10 mg/L). Chest radiography results revealed clear lungs. Thyroid function tests showed suppressed levels of thyroid-stimulating hormone (TSH), elevated thyroid hormones levels, suggestive of thyrotoxicosis and also negative antithyroid antibodies (Table 1).

Investigation findings on admission Table 1

Test Name	Value	Normal
TSH	<0.05	0.25-5 (uiU/l)
FT3	7.7	4-8.3 (pmol/l)
FT4	23.5	10.6-19.4 (pmol/l)
ESR	120	2-13 (mm/h)
CRP	130	0-10 (mg/l)
Fibrinogen	601	150-400 (mg/dl)
TPOAb	2.2	0-8 (UI/ml)
TgAb	25,9	2.5-77 (ng/ml)
WBC	10.76	4.6-10.0 (x10^3)
PLT	636	150-400 (x10^3)
Hb	9.6	11.7-15.5 (g/dl)

A thyroid ultrasound revealed a heterogeneous thyroid gland with bilateral patchy ill-defined hypoechoic areas, suggestive of subacute thyroiditis. (Figure 1). Cervical lymphadenopathy of 4 mm was noted. Reactive left paratracheal lymph nodes were noted without pathological nodes elsewhere in the neck.

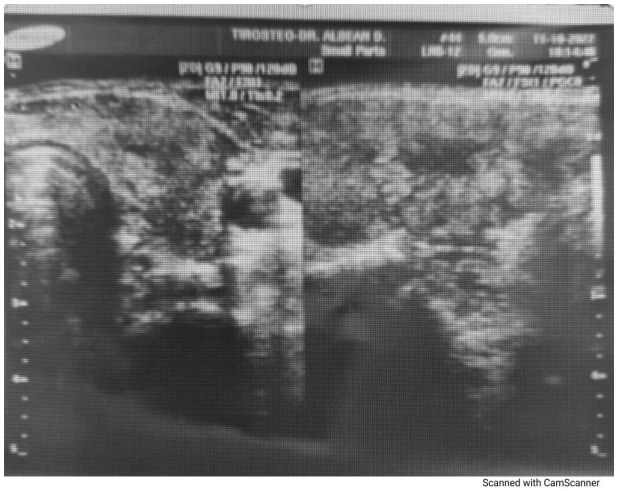

Fig. 1. *Ultrasonography of the thyroid gland*

Bacteriological examinations, including blood culture, urine culture, pharyngeal exudate, and nasal exudate, were negative. Serological tests for hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus, cytomegalovirus, and human immunodeficiency virus were also negative. Antinuclear antibodies and rheumatoid factor tests returned negative results. The IgM test for SARS-CoV-2 was borderline, while the IgG test was positive. Thyroid scintigraphy with Tc99m reveals almost absent uptake at the thyroid level, and low technetium uptake, consistent with the diagnosis of thyroiditis (Figure 2).

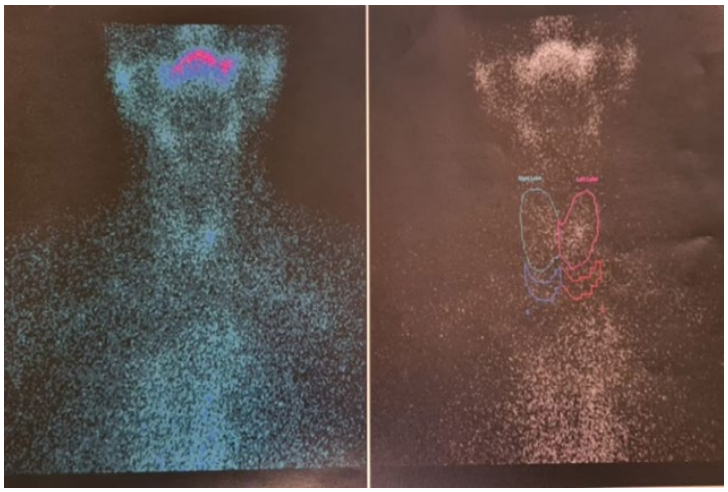

Fig. 2 *Scintigraphy of the thyroid gland*

The patient received corticosteroid treatment associated with beta-blockers (Metoprolol) resulting in the complete resolution of symptoms and a reduction in inflammatory markers, within ten days after the SAT diagnosis. However, the patient continued to exhibit elevated levels of thyroid hormones. (Table 2)

Subsequently, she was discharged from the hospital with tapering doses of methylprednisolone for one month. Her thyroid function tests settled over a period of four weeks. During follow-up at the endocrinologist, she developed subclinical hypothyroidism, and low-dose thyroxine treatment was started with 25ug daily.

Investigation findings on discharge Table 2

Test Name	Value	Normal Value
TSH	<0.05	0.25-5 (uiU/l)
FT3	3,68	4-8.3 (pmol/l)
FT4	26.5	10.6-19.4 (pmol/l)
ESR	54	2-13 (mm/h)
CRP	20	0-10 (mg/l)
Fibrinogen	458	150-400 (mg/dl)
WBC	16.626	4.6-10.0 ($x10^3$/ul)
PLT	632	150-400 ($x10^3$/ul)

3.1.2. Case 2

In May 2023, a 39-year-old female presented to the emergency room of the Clinical Hospital of Pneumology and Infectious Disease of Brasov. She was healthy at baseline and unvaccinated for COVID-19. She complained of odynophagia, pain in the anterior neck region, and a low-grade fever with an onset of two weeks. Despite being prescribed amoxicillin/clavulanate by her primary care physician for a duration of seven days, the symptoms did not improve. The patient's history strongly indicated that she had contracted COVID-19 at the beginning of April 2023. During that time, she experienced a loss of smell and a severe dry cough that persisted for two weeks. These symptoms were also observed in other family members. At the time of her visit time, the patient had not undergone testing for COVID-19, but in retrospect, it appeared to be the likely diagnosis.

In May 2023, she noticed pain in her anterior neck, in the region of the thyroid gland, which radiated to the jaw and head. Additionally, she noticed swelling in her neck, and she sought an examination from her primary care doctor, who recommend treatment with amoxicillin/ clavulanate. Despite treatment, she continued to experience neck pain accompanied by fatigue and a persistent feeling of needing to clear her throat. She also experienced symptoms such as tiredness, mood swings, irritability, tremors, and palpitations. Subsequently, she presented to our hospital where a clinical examination and laboratory tests, including the thyroid function tests, confirmed a diagnosis of SAT with thyroid over-activity.

The laboratory tests showed elevated levels of both free thyroxine and free triiodothyronine, significantly low serum levels of thyrotropin (TSH), elevated

thyroglobulin level, and high inflammatory markers. Antibodies to thyroglobulin (TgAb), peroxidase (TPOAb), and TSH-receptor were negative (Table 3). Her COVID-19 antibodies were positive.

Investigation on admission Table 3

Test Name	**Value**	**Normal value**
WBC	7.77	4.0-10.0 (x10³/ul)
ESR	70	2-13 (mm/h)
CRP	21	0-10 (mg/dl)
TSH	<0,05	0.25-5 (uiU/l)
FT3	10,71	4-8.3 (pmol/l)
FT4	40,95	10.6-19.4 (pmol/l)
Thyroglobulin	330,3	1,6-61,3 (ng/ml)
TPOAb	<0,8	0-8 (UI/ml)
TgAb	34,9	0-18 (ng/ml)
TRAb	<0,800	<1,750

A thyroid ultrasound showed a normal-sized thyroid with patchy areas of variably reduced parenchymal echogenicity bilaterally, consistent with the typical ultrasound features of subacute thyroiditis, which was more extensive on the left than the right. No lymph nodes were noted elsewhere in the neck (Fig. 3). She was treated with Ibuprofen 400mg twice daily for seven days. However, due to the persistence of symptoms, she continued to take prednisone 25 mg daily as the starting dose, gradually tapered. Under the corticosteroid therapy, there was progressive resolution of symptoms within two weeks.

The patient will be followed until she completely recovered and all thyroid functional tests normalized.

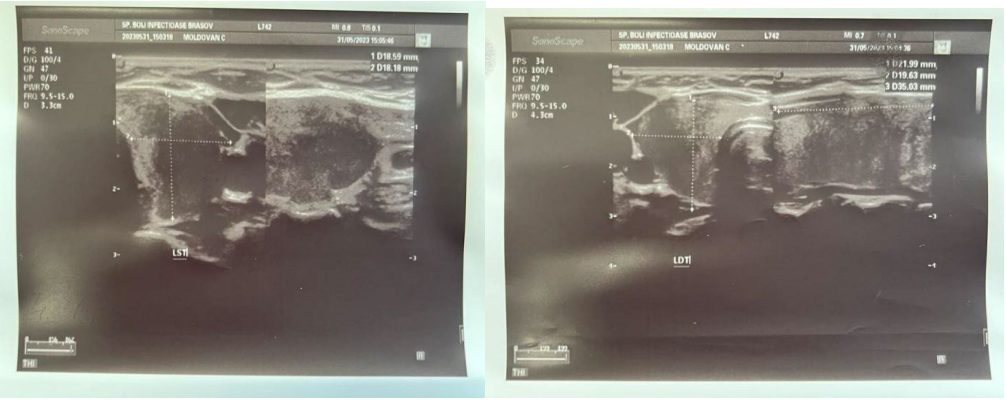

Fig. 3. *Ultrasonography of the thyroid gland*

4. Discussion

Subacute thyroiditis is a self-limiting inflammatory disorder of the thyroid. The most common aetiology of subacute thyroiditis is an inflammatory process caused by viral infection. [12] The viral aetiology is supported by the onset of SAT after an upper respiratory infection and its occurrence during viral outbreaks [7]. Evidence for viral infection in SAT has been linked to mumps virus, coxsackie virus, adenovirus, Epstein-Barr virus, rubella, and cytomegalovirus, though a specific viral cause is not always found [5],[9]. It would appear that SARS-CoV-2 should be added to the list of viruses causing SAT [10],[11],[13].

The analysis of the specialized literature related to thyroid dysfunction in patients with COVID-19 shows that the thyroid gland and the hypothalamus-pituitary-thyroid axis could be a target for SARS-CoV-2 [5],[10],[14]. SARS-CoV-2 has been found to exhibit a high affinity for ACE2 receptors, with the testis showing the highest concentration of these receptors, followed by the thyroid [14]. Interestingly, the binding level in the thyroid appears to be even higher than that in the lung. This suggests that thyroid cells could potentially serve as a target for viral entry, providing a possible explanation for the observed association between thyroid dysfunction and COVID-19. [15], [16], [17], [18].

The association between COVID-19 and subacute thyroiditis may also be influenced by the development of a phenomenon known as the cytokine storm, which is primarily characterized by increased levels of interleukin-6 (IL-6) during SARS-CoV-2 infection. This mechanism can be considered another contributing factor to the observed link between COVID-19 and subacute thyroiditis. [19].

Subacute thyroiditis typically manifests with symptoms such as neck pain, fever, and thyrotoxicosis. Laboratory tests often reveal elevated thyroid hormones and decreased TSH levels. Ultrasound assessment plays an important role in the diagnosis and monitoring of subacute thyroiditis as it can detect focal or diffuse hypoechogenic areas [20]. Additionally,

thyroid iodine uptake is usually reduced.

The management of subacute thyroiditis primarily involves symptomatic therapy, nonsteroidal anti-inflammatory drug, or prednisone administration. NSAIDs can be given to patients with mild and moderate forms of the disorder [12]. In severe forms, therapy with corticosteroids generally provides rapid relief of symptoms within 24 – 48 h. [12]

Patients will have an initial phase of hyperthyroidism (thyrotoxicosis) attributed to the release of preformed thyroid hormone from damaged thyroid cells. This is followed by hypothyroidism, when the thyroid stores are depleted, and then eventual restoration of normal thyroid function. Some patients may develop permanent hypothyroidism. [15]

In our reported cases, the patients exhibited suppressed TSH levels, elevated levels of free thyroxine, and elevated inflammatory markers. The first patient presented with a prolonged febrile syndrome, which was later diagnosed as subacute thyroiditis. Both patients reported a viral illness approximately six weeks prior, compatible with COVID-19, although they were not tested for it at the time. The symptoms resolved with symptomatic treatment. In the first case, the presence of anaemia and thrombocytosis necessitated follow-up by the haematology department. The patient underwent a bone marrow biopsy, ruling out any haematological disorder, and after three months of follow-up, laboratory analyses returned to normal. Both patients required corticosteroid therapy to control the inflammatory process, with favourable evolution.

5. Conclusion

Subacute thyroiditis is a potential complication associated with the SARS-CoV-2 virus. The thyroid inflammation can influence the short-term evolution but also the long-term quality of life. By understanding this, we can act accordingly to improve progress and minimize long-term effects. Clinicians should stay vigilant about this self-limiting condition, which in general only requires consideration of non-steroidal anti-inflammatory agents or prednisolone for more severe or persistent pain. However, future studies are needed to develop more precise clinical guidelines for its management.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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