Subacute Thyroiditis Complicating COVID-19 Infection

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Sage

ABSTRACT: Subacute thyroiditis (SAT) is a self-limited inflammatory disease and a rare cause of thyrotoxicosis. Although the exact etiology of SAT is not sufficiently understood, it is generally associated to viral infections. Current evidence highlights that SAT may be a potentially uncommon manifestation of ongoing Coronavirus disease 2019 (COVID-19) infection or a post-viral complication of the disease. Despite that SAT is a rare manifestation associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease both in ongoing and resolved COVID-19 infection, the ever-increasing numbers of COVID-19 patients strengthens the possibility that this particular disease entity will be of more immediate concern in the future. The current work aims to summarize the approach of SARS-CoV-2-associated SAT, present its pathophysiology, outline current research evidence found in the literature, and discuss potential differential diagnoses and diagnostic dilemmas through an illustrative case.

KEYWORDS: COVID-19, endocrinology, hyperthyroidism, thyroid disease, subacute thyroiditis

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Introduction

Accumulating evidence highlights a causal relationship between SARS-CoV-2 infection and various thyroid disorders including subacute thyroiditis (SAT), nonthyroidal illness syndrome (NTIS), and autoimmune thyroid diseases, such as Graves' disease (GD) and Hashimoto's thyroiditis.[1] Recent research data demonstrate SAT as a potential manifestation of ongoing COVID-19 infection or a post-viral complication of the disease.[2] Direct viral toxicity and post-viral inflammatory reaction—the so-called "cytokine storm," term which describes a systemic hyperinflammatory status resulting in pleomorphic thyroid disturbances—may represent the major pathogenetic mechanisms of the disease. Indeed, it is well established that the mRNA of the SARS-CoV-2 angiotensin-converting enzyme 2 receptor (ACE2) is expressed in thyroid cells, so the thyroid may be susceptible to SARS-CoV-2 infection.[3-6] However, because clinicians focus greatly on COVID-19 infection, this complication can be largely ignored or misinterpreted. Indeed, until May 30, 2022, only 16 case reports, 5 case series, 2 cross-sectional studies, and one prospective study of a total of 69 patients had been published.[3,7] We, therefore, report an unusual case of SARS-CoV-2-associated SAT and having it as starting point we condense the latest relevant literature and present its pathophysiology aiming to contribute to the recognition and management of SARS-CoV-2-associated SAT in daily, clinical practice.

Case Presentation

A 44-year-old previously healthy woman reported progressive symptoms of neck pain, headache, asthenia, insomnia, hands tremor, hyperhidrosis, diarrhea, weight loss of 8 kg, and palpitations following mild COVID-19 disease manifested 1 month earlier. These symptoms began 14 days after her positive test result but regressed completely within 1 week of symptomatic therapy. Anamnestically, the patient was pregnant with partum 1 year earlier, and thus immunity from measles, mumps, and rubella had already been tested. Moreover, medical history was not suggestive of iodine exposure.

Findings and diagnostics

Palpation of the neck was painful but revealed no nodules. The thyroid gland was slightly enlarged, making it difficult to swallow. The skin was warm and moist on all parts of the body and a fine finger tremor was observed. Laboratory findings showed a suppressed thyroid-stimulating hormone and markedly elevated free thyroid hormones with increased inflammatory parameters (Table 1). Thyroid ultrasonography showed an enlarged thyroid gland of up to 50 ml with an inhomogeneous, predominantly hypoechogenic structure, and mild hyperperfusion over the entire organ (Figures 1 and 2).

We interpreted the findings in the context of an SAT and we started steroid therapy. Under steroid therapy (30 mg prednisone daily for 2 weeks followed by weekly reduction of the dose by 2.5 mg), the parameters of thyroid function and inflammation levels were clearly regressive over the course of 7 days (Table 1). We interpreted the initially elevated thyroglobulin level as part of inflammatory damage of the thyroid. A follow-up after 6 weeks showed a euthyroid metabolic state with normalization of TSH and free thyroid hormones. The patient reported feeling well; initial symptoms had completely regressed, and she was able to return to her everyday life

Table 1. Laboratory parameters

LABORATORY RESULTS SYSTÈME INTERNATIONAL (SI)	STANDARD VALUES (REFERENCE RANGE)	FIRST VISIT	1 WEEK LATER	6 WEEKS LATER
Leukocytes (G/L)	3.50-10.00	9.87	10.62	10.18
Erythrocyte sedimentation rate mm (1 h)		98		
C-reactive protein (mg/L)	⩽ 5	78	1.8	1.7
Thyroid-stimulating hormone (TSH) mIU/L	0.27-4.20	0.005	0.006	2.1
Triiodothyronine, fT3 (pmol/L)	3.1-6.8	15.5	6.72	4.01
Free thyroxine, fT4 (pmol/L)	12-22	51.8	35.1	14.6
Antibodies to thyroid peroxidase, Anti-TPO Abs (kIU/L)	<60			<28
Antibodies to TSH-Receptor, TRAb (CMIA)(kIU/L)	<1.8			<0.9
Thyroglobulin (µg/L)		70		8.1

Thyroglobulin reference values:
Euthyroidism, normal TSH: <58 µg/L.
After total thyroidectomy, TSH suppressed: <2.0 µg/L.

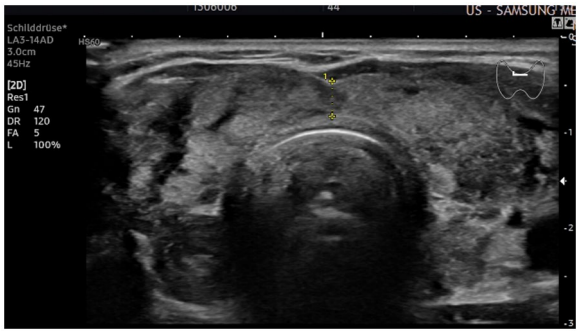

Figure 1. Thyroid sonography at the time of initial presentation. A voluminous thyroid gland with a highly inhomogeneous, predominantly hypoechogenic structure can be seen.

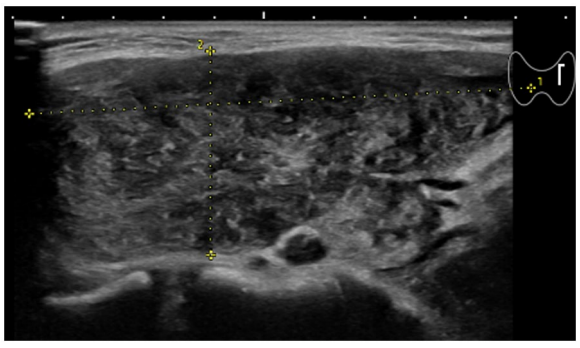

Figure 2. Close-up of the left thyroid lobe at the time of initial presentation.

without restrictions. The corticosteroid therapy was administrated for 12 weeks in total.

Discussion

Recent research evidence demonstrates that SAT may complicate COVID-19 infection either during an ongoing COVID-19 infection or as a post-viral complication of the disease, particularly in individuals with specific genetic backgrounds.[2,7,8] Indeed, accumulating research highlights that individuals who are carriers of certain Human Leukocyte Antigens (HLA) (eg, HLA-B35, HLA-B67, HLA-B15/62, and HLA-Drw8) present enhanced predisposition to develop SAT.[9] COVID-19 can affect the thyroid gland by various pathogenetic mechanisms; however, direct cytotoxic effects and pathologically enhanced post-viral systemic inflammatory and immune responses may represent the main pathogenetic mechanisms of the disease (Figure 3).[10] Rotondi et al demonstrated that the mRNA of the SARS-CoV-2 receptor ACE2 is expressed in thyroid cells and as such, the thyroid may be susceptible to SARS-CoV-2 infection.[3] Because S protein of SARS-CoV-2 recognizes ACE2 combined with the transmembrane protease transmembrane serine protease 2 (TMPRSS2) to enter the host cells, the possibility of direct virus toxicity explaining the pathogenicity of the disease is further supported.[10] Moreover, similar to other coronaviruses, for example, SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), COVID-19 infection is strongly associated with a cytokine storm syndrome frequently accompanied by lymphopenia. A variety of detrimental effects of hypercytokinemia on human organs and systems have been previously described and include cellular damage, arterial and venule thrombosis, vasculitis, and hypoxia-induced organ dysfunction.[11] It appears, however, that while the cytokine storm can largely explain the nonthyroidal

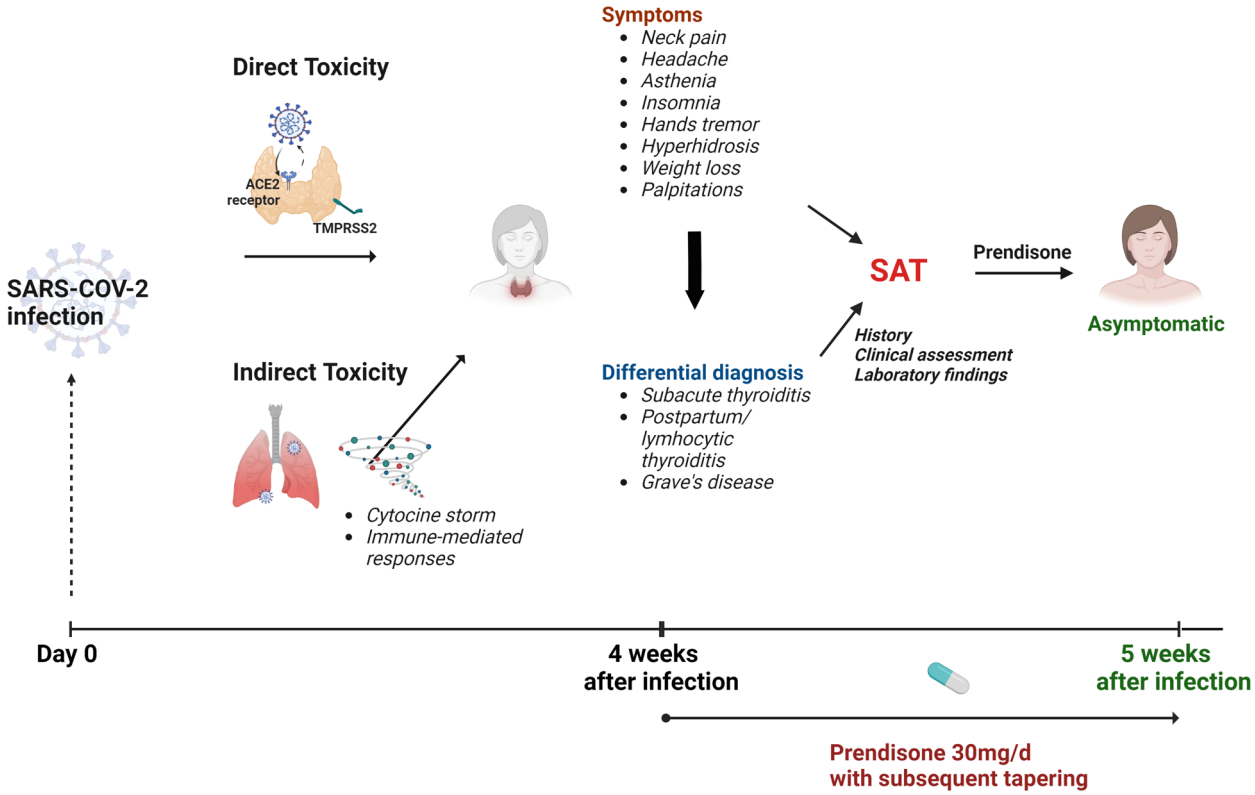

Figure 3. Simplified schematic representation of the pathophysiology of SARS-CoV-2-associated SAT. In addition, presentation of clinical symptoms and signs, differential diagnosis, and therapy of our patient.

illness syndrome in patients with COVID-19, it is insufficient to solely explain the thyrotoxic effects, at least in humans. Therefore, it has been proposed that the abnormal immune-mediated responses, involving both the adaptive and innate immune systems, can partially explain the thyrotoxic effects that occur in the post-COVID-19 infection period.[12]

SAT is a clinical diagnosis, which typically presents anterior neck pain—commonly radiating to the jaw or ear—asthenia/malaise, anorexia, low-grade fever, and mild hyperthyroid symptoms, such as palpitations. The clinical examination usually shows tenderness and an enlarged and painful thyroid gland (Figure 3).[2,13] Similar symptoms are observed in patients with COVID-19-related SAT, however, there are reports that the clinical presentation of SAT associated with SARS-CoV-2 is more severe compared to that of other etiologies.[14] Moreover, it should be taken into account that the clinical picture of the disease may deviate from the typical one. This is especially the case in hospitalized patients either because these patients are often on steroid treatment or because their symptoms may be overshadowed by the symptoms of the SARS-CoV-2- infection leading to oversight of SAT and a worse prognosis.[6] Moreover, physicians should be aware of the clinical entity of painless thyroiditis in the context of SARS-CoV-2 infection. Consistently, a recent combined retrospective–prospective study highlighted that patients with painless SAT showed earlier presentation, more severe symptoms of hyperthyroidism, and exhibited higher CRP, interleukin-6 (IL-6), and neutrophil-lymphocyte ratio (NLR), and lower absolute lymphocyte count compared to patients with painful SAT. In addition, the authors reported significant correlations of IL-6 with free and total T4 and free and total T3, indicating the devastating properties of cytokines that may play a cardinal role in the pathogenesis of painless SAT.[1] The clinical examination of our patient revealed a painful and voluminous thyroid gland and moist and warm skin.

Although SAT is largely a clinical diagnosis, biochemical and imaging tests can provide additional information and strengthen clinical suspicion.[13,15] Thyroid function tests usually show a suppressed TSH and elevated total and free thyroxine (fT4) and triiodothyronine (fT3) levels with a high fT4/fT3 ratio. Inflammatory markers, such as erythrocyte sedimentation rate (ESR), white blood cell (WBC) counts, and C-reactive protein (CRP), are usually increased.[16] Brancatella et al studied the thyroid function in 18 patients with SARS-CoV-2-associated SAT during the period 2016 to 2019 and found significantly higher levels of fT4, CRP, and thyroglobulin compared to patients with SAT caused by other viruses.[14] Similarly, in our patient, we found a suppressed TSH and markedly elevated free thyroid hormones and thyroglobulin with increased inflammatory parameters, findings which are in accordance with the biochemical characteristics highlighted. Differentially, GD following a COVID-19 infection could

have been considered, but this was unlikely given the negative anti-TSH-receptor antibodies[17] (Figure 3). Although we could not make a definite differential diagnosis from antibody-negative GD, this eventuality was, however, assessed also as unlikely given the history of viral infection, the clinical presentation with the painful thyroid gland and the absence of exophthalmos, and the rarity of antibody-negative Grave's disease. Indeed, a study, which analyzed 255 patients diagnosed as having GD based on clinical manifestations and laboratory findings, demonstrated that TRAb were detectable in 98.7% of patients with GD.[18] Because targeted antiviral treatment is not available and given the diagnosis of COVID-19, we did not perform an additional diagnostic evaluation in order to identify the etiology of the viral infection[13,15,19,20] However, there was no evidence of an acute infection with influenza A and B, adenovirus, and human enterovirus on admission. Moreover, because the patient was pregnant with partum 1 year earlier, immunity from measles, mumps, and rubella had already been tested. In addition, iodine exposure could be anamnestically excluded. Furthermore, due to the medical history, clinical presentation, and laboratory findings postpartum/lymphocytic thyroiditis could also be excluded. Therefore, in our case SARS-CoV-2 was the most probable viral trigger of subacute thyroiditis. Our patient underwent additional thyroid ultrasound in order to have a comprehensive evaluation of the disease entity. We found a voluminous, and inhomogenous thyroid gland with a predominantly hypoechogenic structure and partial hypervascularization. These findings are consistent with ultrasonographic features demonstrated by previous studies in patients with SAT associated with COVID-19 infection as well as in patients with SAT of other etiology.[11,19] Although treatment with steroids and non-steroidal anti-inflammatory drugs is strongly debated due to the self-limited nature of the disease,[16] we decided in favor of steroid administration given the patient's discomfort. We started with an initial dose of 30 mg/day of prednisone, which was gradually tapered over a period of 12 weeks. Indeed, until now there are no formal treatment guidelines in order to manage patients with SAT. The suggested therapy options deviate between publications aiming primarily at reducing the severity of the disease and limiting the inflammatory reaction and the frequency of relapses to avoid permanent hypothyroidism. Primary treatment options include beta-blockers, non-steroidal anti-inflammatory drugs (NSAIDs), and steroids.[21] NSAIDs administration can be considered in cases of mild to moderate disease. Additionally, the American Thyroid Association recommends the administration of prednisolone at a dose of 40 mg per day for patients with poor response to the initial treatment with NSAIDs or for patients with severe disease.[22,23] However, even in patients receiving steroid treatment, the high rates of relapse when tapering the dosage create concern, as well as their side effects, which may develop even during a short treatment period.[21] Similar to other reported cases,[7] our patient showed a dramatic clinical improvement under corticosteroid therapy and the thyroid and inflammation levels were clearly regressive over a course of 7 days. In line with previously published recommendations suggesting a gradual taper of corticosteroids over a period of 2 to 4 weeks or longer and given the high recurrence rate of SAT as the dose of corticosteroid is reduced,[21] and the absence of official suggestions regarding the duration of corticosteroid therapy in patients with SARS-CoV-2-associated SAT, we decided in favor of a longer tapering, that is, for a period of 12 weeks in our case. Moreover, we performed a clinical-laboratory follow-up 6 weeks after the diagnosis of SAT and found a normalization of TSH as well as normal free thyroid hormones, while the patient remained clinically asymptomatic 1 year after the initial episode of SAT.

In conclusion, we diagnosed a case of COVID-19-induced SAT based on clinical symptoms, typical laboratory constellation, and classical ultrasound findings. Moreover, the absence of anti-TSH receptor and thyroperoxidase antibodies supported this diagnosis further. Despite that SAT is an uncommon complication of SARS-CoV-2 infection, the ever-increasing number of COVID-19 patients strengthens the possibility that this particular disease entity will be of more immediate concern in the future. Indeed, as mentioned above, SARS-CoV-2 shows an enhanced affinity for the thyroid gland, which seems to be stronger than the one corresponding to the lung, making testing for COVID-19[24]—even without clinical evidence of SARS-CoV-2-infection—a reasonable consideration in patients with SAT, especially in critically ill patients. However, because the outbreak of the SARS-CoV-2 pandemic is relatively recent, the available data for the establishment of a relationship between COVID-19 and thyroid dysfunction are limited. Further evidence is needed to be able to support a causal link between them and to propose specific protective and therapeutic strategies with high confidence. In addition, even though international guidelines do not recommend testing of thyroid function in the context of a SARS-CoV-2 infection, taking into account the simplicity, the availability, and the low cost of these laboratory investigations, evaluation of thyroid function should be included in the assessment of patients with COVID-19—especially those who are treated in intensive care units—in light of the evidence indicating a possible link between SARS-CoV-2 infection and thyroid illness. Moreover, because subacute thyroiditis seems to be also associated with other viral infections, the same diagnostic strategy could be considered for other viruses as well.[1,25] In addition, due to the spread of SARS-CoV-2 disease, it has been observed that clinicians focus greatly on COVID-19 infection, which could affect the correct diagnosis of other[26] or co-existing diseases, for example, SAT. As such, physicians' vigilance constitutes a fundamental part of patients management.

Further studies are needed to improve our understanding of SAT pathogenesis in COVID-19 patients and optimize diagnostic algorithms and therapeutic procedures.

Learning Points

- SAT is largely a clinical diagnosis, biochemical and imaging tests can provide additional information and confirm clinical suspicion
- SAT may be a potentially uncommon manifestation of ongoing COVID-19 infection or a post-viral complication of the disease.
- SAT is a self-limiting condition, treatment with steroids and non-steroidal anti-inflammatory drugs may be supportive.

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Figure 3 created with BioRender.com

Author's Contributions

The study was designed by Katrin Henke and Natalia Rudovich. Katrin Henke and Natalia Rudovich were involved in the diagnosis and management. Katrin Henke, Jonas Odermatt and Mairi Ziaka searched the articles and drafted the manuscript, to which Natalia Rudovich contributed and helped to revise. All authors read and approved the final manuscript.

Informed Patient Consent for Publication

Written informed consent was obtained from the patient for publication of this case report.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

Ethical Approval

The project did not meet the definition of human subject research.

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