

Subacute Thyroiditis and Thyroid Inflammatory Nodule Secondary to COVID-19: A Primary Care Case Report

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Case Report

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Abstract

Objective: To describe a case of subacute thyroiditis (SAT) secondary to COVID-19 in the primary health care (PHC) setting.

Case description: A 51-year-old woman was treated in a PHC facility for flu-like symptoms for 5 days and pain in the lower neck. Symptomatic drugs were prescribed, and the patient was tested for COVID-19. The patient reported a personal history of Chagas disease with no disease manifestation. On reassessment, the patient presented a painful edema on the thyroid gland, dysphagia and improvement in flu-like symptoms. Nonsteroidal anti-inflammatories were prescribed, and thyroid function analysis and inflammatory markers were collected. Reassessment after one week showed positive PCR-rt for COVID-19, partial improvement of neck pain, alterations in thyroid hormone tests (suppressed TSH and slightly elevated T4) and elevated C-reactive protein. Thyroid gland ultrasonography was requested, and anti-thyroglobulin, anti-TPO antibodies and prednisone were prescribed. Anti-thyroglobulin was positive, and anti-thyroid peroxidase antibodies were negative; thyroid ultrasonography showed a solid nodule in the left lobe (approximately 4 cm), classified as TIRADS-4. The patient was sent to the Endocrinology Service, and a thyroid fine needle aspiration was requested. Ultrasonography prior to the exam evidenced a complete regression of the nodule, which was diagnosed as an inflammatory pseudo nodule.

Conclusion: We presented the case of a patient who was treated in a PHC facility for rare findings of SAT secondary to mild COVID-19, concomitant with a thyroid nodule that had complete remission after approximately three months and was interpreted as an inflammatory pseudo nodule secondary to SAT. PHC professionals should be aware of this condition and conduct adequate follow-up of these patients.

Background

COVID-19 disease emerged in Wuhan, China, in December 2019. On March 11, 2020, when there were 118,000 confirmed cases in 114 countries, Medical Director General of the World Health Organization (WHO) Tedros Adhanom Ghebreyesus officially declared COVID-19 a pandemic (1). The virus causing the disease was severe acute respiratory syndrome virus 2 (SARS-CoV-2), a single-stranded, enveloped RNA virus of the beta-coronavirus family (1, 2).

COVID-19 is recognized as a disease that severely affects the pulmonary system; nonetheless, it is actually a systemic disease with the potential to affect multiple organs and systems, causing acute and chronic conditions (1-4). The pituitary-thyroid axis is a possible target of the SARS-CoV-2 virus, as well as the thyroid gland (5). Thyroid gland involvement has emerged as a very common event in the course of COVID-19 (4).

Subacute thyroiditis (SAT), also called De Quervain's thyroiditis, is a relatively rare condition of the thyroid; however, it is a common cause of pain in the thyroid gland. It is associated with viral infections such as measles, rubella, coxsackie and adenovirus, due to viral toxicity and its inflammatory response to the virus (5). It is a self-limited behavior with a good prognosis (6-10). Studies have been published showing

the relationship of thyroid disease and COVID-19, particularly isolated cases of patients with SARS-CoV-2 infection developing SAT. These cases, even if sporadic, serve as an alert for COVID-19 as a possible etiology of the disease (5, 11, 12), as well as the possibility of other presentations of this condition, as in this case, an inflammatory nodule simulating a tumor. The aim of the present study is to present a case report of a patient with SAT manifestations associated with an inflammatory pseudo nodule, secondary to COVID-19 with a mild course and favorable evolution.

Materials And Methods

The patient read and signed an informed consent form and authorized publication of the data. The study information was obtained by reviewing the electronic medical records, patient interviews, photographic registers of patient exams and literature reviews (Protocol Number of the Research and Ethics Committee of Faculdade São Leopoldo Mandic: 5.250.293).

Case Report

A 51-year-old female patient was seen at our primary health care (PHC) service with symptoms of odynophagia, malaise, headache, and chills for 5 days. She did not report cough or gastrointestinal symptoms or a loss of smell or taste. She reported a history of Chagas disease with no clinical manifestation. On physical examination, she was in good general condition, with normal cardiology and respiratory examinations, and mild hyperemia in the tonsil pillars. A polymerase chain reaction-rapid test (PCR-rt) for SARS-CoV-2 was collected, analgesics were prescribed, and she was asked to return in a week for follow-up.

On reassessment after 5 days, a PCR-rt for SARS-CoV-2 was positive. She reported improvement of previous symptoms but persistent odynophagia and new pain located on the left side of the lower neck two days prior to the visit. Physical examination showed a painful goiter mostly in the left lobe, and there were no palpable lymph nodes on examination. SAT was suspicious, and thyroid function tests (TSH, free T4, T3 and C-reactive protein (CRP)) were requested. Nonsteroidal anti-inflammatories were prescribed for 5 days, and a one-week follow-up visit was scheduled.

On reassessment after 7 days, the patient reported partial improvement of lower neck pain but also headache and night tremors. The serum evaluation tests showed T3 1.9 pg/ml, T4 17.9 mg/dl, free T4 (T4 L) 3.32 ng/dl, TSH 0.03 mU/L and PCR 93.63 mg/L. Serum anti-thyroglobulin and anti-thyroid peroxidase (anti-TPO) antibodies were requested, as well as thyroid ultrasonography (USG) for differential diagnosis, and prednisone was prescribed for 5 days.

Anti-thyroglobulin and anti-TPO antibodies were 16.8 UI/mL and <9 U/ml, respectively. Thyroid USG showed a solid nodule in the left lobe occupying the entire left lobe, measuring 4.3X1.6 cm, larger in width than in height, with well-defined margins and without calcification, with discrete central and peripheral vascularization, as measured on Doppler and classified as TIRADS 4. The patient was referred to the

endocrinology service for cytological investigation. During guided thyroid USG to perform the cytological aspiration, the nodule had complete remission and no signs of inflammation, leading to the diagnosis of pseudoinflammatory nodules secondary to SAT.

Development And Discussion

COVID-19 is the most rapidly progressing and lethal infectious disease since the Spanish Flu of 1818-1820 (4). The disease has its main clinical manifestation in the respiratory system, causing a flu-like syndrome in most cases, which can evolve to interstitial pneumonia. It also has the potential to infect other organs and systems, such as the neurological, cardiovascular, gastrointestinal and endocrine systems (3, 4, 13).

The virus invades the cells through the spike protein, which binds to angiotensin-converting enzyme-2 (ACE2) receptors, which regulate the renin-angiotensin-aldosterone (RAAS) system, presented in large profusion on the surface of human epithelial cells (3, 4, 12, 14). ACE2 receptors (genetically susceptible to infection by SARS-CoV-2) are abundant, particularly in the follicular cells of the parenchyma of the thyroid gland (4). Injury to the endocrine system can occur directly due to the cytopathological toxicity of the virus in the gland or indirect injury through the involvement of the hypothalamic-pituitary axis by systemic inflammation from the secretion of chemokines and cytokines, induced autoimmune injury and/or vascular injury (3). In a study performed analyzing necropsies of patients infected with SARS-CoV-2 carried out in 2007, histological analysis revealed severe lesion of the follicular cells with destruction of the follicular epithelium, spoliation of epithelial cells, capillary congestion of the connective tissue between the follicles, as well as interstitial fibrosis (15). Studies have shown a reduction in TSH and a relationship between thyroid dysfunction and COVID-19 severity (3). Lania et al. (16) verified an inverse relationship between TSH and interleukin 6 (IL-6) levels, confirmed in multivariate analyses, and an increase in hospital mortality in patients with thyrotoxicosis and TSH <0.1 mU/L. Gao et al. (17) observed that free T3 levels were negatively correlated with CRP (C-reactive protein), IL-6 and tumor necrosis factor (TNF) alpha.

Subacute or de Quervain's thyroiditis is a granulomatous and nonsuppurative inflammatory disease of the thyroid that manifests as pain in the topography of the gland and is associated with systemic manifestations such as fever, fatigue, and myalgia (10, 18). SAT is an infrequent thyroid disorder; however, it is the most common cause of thyroid gland pain (6, 11). Fatourehchi et al. (19), in a study carried out in a Minnesota county (USA), estimated the prevalence of TSA to be 4.9/100,000 per population. It can also manifest with symptoms of thyrotoxicosis, resulting from the extravasation of thyroid hormones secondary to injury to the gland, and even hypothyroidism in cases where the injury results in permanent gland damage (18, 20). Ohsako et al. (21) observed that although there is production of antibodies against the thyroid gland in SAT, it is a transient phenomenon and results from the leaking of antigens after the destruction of thyroid follicles and therefore does not represent a true autoimmune disease. Furthermore, a genetic predisposition to SAT was associated with the presence of

the human leukocyte antigen (HLA) Bw35 (12, 21). SAT is more prevalent in females, with a ratio of 3-7:1 in relation to males, ages 20 to 60 years, and is considered rare in children and elderly individuals (18).

The pathophysiology of the disease involves an inflammatory reaction secondary to a previous viral infection of the upper airway, and many viruses have been associated with SAT (5, 18). The histological changes in the initial phase are in accordance with the hyperthyroid state, caused by gland destruction, colloid and hormone leakage and neutrophilic invasion with the development of microabscesses. In the transition from acute to subacute inflammation, there is lymphocytic and histiocytic invasion, and the presence of multinucleated giant cells infiltrated in the colloid is noticeable (18). The late phase is distinguished by interfollicular fibrosis and corresponds to the hypothyroidism phase. Fine needle aspiration (FNA) may vary depending on the stage of the disease, and it may show a mixture of multinucleated giant cells, epithelial granulomas and inflammatory residues in the middle of the colloid. Multinucleated cells are the “thyroiditis giant cells” and are the hallmark of the disease. However, they can be found in other conditions, such as sarcoidosis and infections (by fungi and mycobacteria), and are a nonspecific finding of papillary thyroid carcinoma (18).

Generally, the disease develops within two to eight weeks after viral infection and may evolve with a fluctuating pattern between 3 and 6 weeks, with gradual or sudden onset (11, 18). The patient in this report presented a painful goiter earlier than usual (eight days) and a relatively abrupt onset associated with mild symptoms of thyroiditis. She also presented TSH suppression, an increase in T4 and T4 L values, and a marked increase in inflammatory markers. One of the first cases of SAT associated with COVID-19 was reported by Brancatella et al. (6) in an 18-year-old woman with fever, neck pain and palpitations 15 days after having tested positive for SARS-CoV-2 and mild symptoms of COVID-19. Brancatella et al. (20) also published a series of four cases in patients with mild manifestations of SARS-CoV-2 infection. Two patients had severe gland pain, all patients had symptoms of thyroiditis, and one developed atrial fibrillation requiring electrical cardioversion. Two patients developed subclinical hypothyroidism after treatment. Echographic thyroid alterations were also described in all patients, but no description of nodules mimicking a thyroid tumor was found. It is important to highlight that thyroiditis and thyrotoxicosis were present in critically ill patients, also as painless manifestations, probably due to the use of pain killers (3, 16).

The thyroid gland may also present with symmetrical or asymmetrical enlargement and stiffness. Thyroid ultrasonography changes are common in thyroiditis and may have a polymorphic presentation. Although the applicable methodology is to perform ultrasonography, it also depends on the examiner's interpretation, which makes it susceptible to variations in the exam description. Thyroid nodules (TNs) are increasingly common findings in clinical practice, surpassing Graves' disease. The prevalence of TN in the adult population in clinical evaluation is estimated at 3-7%, and with ultrasound, it increases to 13-67% (18). There are several causes for the formation of TN, including iodine consumption, exposure to radiation, tobacco consumption and mainly chronic inflammation; further, a positive association has been found between TN and *Helicobacter pylori* infection (22).

Our patient had an ultrasound examination suggestive of a malignant nodule, classified as TIRADS-4. Three months later, on ultrasound to guide fine needle aspiration, the nodule was remitted and assumed to be an inflammatory pseudonodule. Inflammatory pseudonodules are rare, but thyroid ultrasound changes secondary to TSA can sometimes be suggestive of this finding (18, 23). Prajapati et al. (18) evaluated a patient with SAT and a 9x7 mm nodule, classified as TIRADS 6 and Bethesda category 6. She underwent a total thyroidectomy, and in the histopathological analysis, the findings were typical of thyroiditis, with no signs of malignancy. Most likely, in our case report, the time elapsed between ultrasonography assessments (which was approximately three months) associated with correct SAT clinical management enabled nodule remission, thus preventing more invasive procedures and iatrogenic measures. Li et al. (23), in 2014, published a case in which the SAT presented a painful nodule measuring 1.5x0.8 cm as the only clinical finding of thyroiditis, showing that laboratory alterations are not always present. It is also possible that SAT manifests without pain, especially in critically ill patients (18, 23).

The treatment of SAT is based on observational studies and aims to reduce inflammation and control symptoms of hyperthyroidism. It is usually performed with the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids in refractory cases. The prognosis is good, but SAT is a risk factor for developing hypothyroidism and permanent thyroid dysfunction, which requires follow-up. In addition, it is rare but possible to have disease recurrence years after the initial presentation (18). It is important to emphasize that patients with thyroid disorders may have a worse SARS-CoV-2 infection outcome, especially those at high risk of developing severe manifestations (4, 13).

Limitations

Despite the fact that the patient was referred to specialized endocrinology care, due to our high demand and considering the patient's good general condition, follow-up exams were not requested in our service, and visits were planned after six months. Therefore, reassessment of thyroid function was not reported.

Final Considerations

This study presented the case of a patient with rare findings of SAT secondary mild manifestations of COVID-19, concomitant with a TIRADS-4 thyroid nodule that evolved with complete remission approximately three months after the initial presentation and was interpreted as an inflammatory pseudothyroid nodule. The time gap between ultrasonographic exams allowed complete nodule regression, thus avoiding iatrogenic measures. Physicians should be aware of thyroid manifestations and the possibility of SAT secondary to COVID-19, particularly in PHC settings in patients with mild to moderate disease, to allow recognition and adequate follow-up of those cases.

Declarations

TO WHOM REPRINT REQUESTS SHOULD BE ADDRESSED

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