

Subacute (De Quervain) Thyroiditis During the COVID-19 Pandemic

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In December 2019, the first case of a pneumonia of an unknown etiology was reported in Wuhan, China. Subsequently, the pathogen was recognized as a new enveloped RNA β -coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19).¹ The disease then spread across the world quickly, and in March 2020, it was declared a pandemic by the World Health Organization.² Since then, heterogeneous clinical developments, ranging from the asymptomatic to the lethal with multiple organ complications, have been observed, and there have been worldwide efforts to better characterize diagnostic and therapeutic methods, risk factors, and possible complications. One of these possible reported complications is the onset of subacute (De Quervain) thyroiditis (SAT).³⁻⁷ SAT is a self-limited inflammatory condition of the thyroid gland that was first described by De Quervain in 1904. The diagnosis is usually made on the basis of clinical data, and the relevant factor is a previous history of viral infection, with influenza, adenovirus, and coxsackievirus being the most common triggers.⁸ The thyroid follicles are often infiltrated, and disruption of the basement membrane of the cells occurs. The thyroid injury is thought to be the result of cytolytic T-cell recognition of viral and cell antigens present in an appropriate complex.⁹

In our experience at 2 major services (a cancer center and a private laboratory) in São Paulo, Brazil, one of the countries most severely affected by the pandemic, we documented 3 cases with a confirmed SARS-CoV-2 infection and a subsequent onset of SAT. The first case was a 34-year-old female who underwent reverse transcriptase–polymerase chain reaction for SARS-CoV-2 as an institutional protocol during the preoperative preparation for breast cancer. The patient had only dyspnea on medium exertion for 2 weeks and had no need for hospitalization. Twenty-eight days after her COVID-19 diagnosis, she developed mild pain in the anterior cervical region and a mild fever (38 °C). An ultrasound examination of the region was performed, with a hypoechogenic area measuring 1.6 cm \times 0.6 cm in the right thyroid lobe. Fine-needle aspiration (FNA) was performed and confirmed SAT. The patient received prednisone at 15 mg/d, and her symptoms disappeared after 4 days. The second case was an asymptomatic 34-year-old female who tested positive for SARS-CoV-2 after her husband had a positive test. She also had no symptoms related to SAT, but a screening neck ultrasound 10 days after her diagnosis showed an irregular and hypoechogenic area in her right thyroid lobe, which was confirmed as SAT by FNA. The patient was previously euthyroid but, after the SAT diagnosis, presented with a high free T₄ level of 1.8 ng/dL. The patient also received prednisone, and in 18 days, the laboratory tests returned to reference values. The third case was a 39-year-old female who presented with only mild symptoms (mild fever and anosmia), which prompted her to be tested for SARS-CoV-2. Twenty-six days after her positive test, she complained of pain in the anterior cervical region, and an ultrasound revealed a solid hypoechogenic nodule in her left thyroid lobe, which was confirmed as SAT by FNA. No information was available for her therapy, but follow-up ultrasound imaging 2 weeks later was normal.

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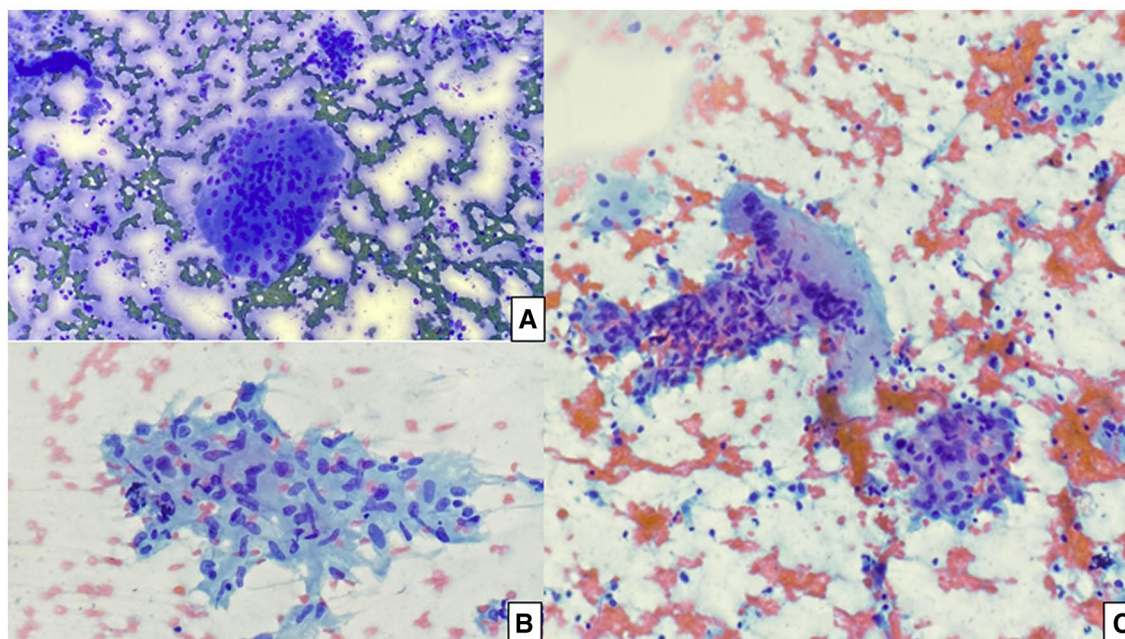


Figure 1. Classic morphology of subacute thyroiditis seen in our cases. (A) Multinucleated giant cell (Diff-Quik, $\times 40$). (B) Granuloma (Papanicolaou, $\times 40$). (C) Scattered epithelioid histiocytes, lymphocytic infiltrate, and a multinucleated giant cell (Papanicolaou, $\times 20$).

The cytological pictures of all 3 cases were very similar, and they all showed clusters of epithelioid histiocytes forming loose granulomas and scattered giant cells amid rare inflammatory and follicular cells (Fig. 1). They were compatible with the classic cytological examination, which typically presents granulomas along with many multinucleated giant cells. Cellularity, however, is variable and depends on the stage of the disease. In the early stages, there are more neutrophils and eosinophils, which are reminiscent of acute thyroiditis. The late stages are hypocellular and show giant cells surrounding and engulfing colloid in addition to epithelioid cells, lymphocytes, and scant degenerated follicular cells.^{10,11}

In previously reported cases in the literature, similarly to our reported experience, the majority of patients were female with an average age of 35 years (range, 18–43 years). Patients were mostly treated with corticotherapy for approximately 4 weeks and had good outcomes.^{3–7,12} The average time between the confirmation of infection and FNA was 25 days (range, 9–42 days).^{4–7,12} The most common symptoms included cervical pain with irradiation to the jaw, asthenia, and palpitation. Importantly, these symptoms could be confused with those commonly associated with sepsis, cardiopulmonary dysfunction, or even progression of the respiratory syndrome caused by

COVID-19⁷; therefore, SAT should be included in the clinical differential diagnosis as a possible complication in these patients.

Although the pathophysiology of possibly COVID-associated SAT has not yet been fully explored, angiotensin-converting enzyme 2 (ACE-2) messenger RNA has been detected recently by reverse transcriptase–polymerase chain reaction in human follicular thyroid cells. Because ACE-2 is the receptor for the cellular entry of SARS-CoV-2, this could partially explain the onset of COVID-19–related SAT by direct viral tissue damage.¹³ As a matter of fact, many changes attributed to SARS-CoV-2 infection have been described in several organs besides the respiratory system^{14–16} (eg, dermatological and cardiac disorders; kidney, neural, and gastrointestinal disorders^{2,16–18}; and diabetogenic effects¹⁹).

To document a possible increase in the cases of SAT during the pandemic period, we also collected data on all cases of SAT diagnosed via FNA in 2019 and 2020. We observed 11 cases in 2019 (0.04% of total cases) and 15 in 2020 (0.07% of total cases). Although there was a slight increase in number potentialized by the decrease in cases in 2020 due to the lockdown established by local authorities,²⁰ this difference was not statistically significant. In addition, laboratory confirmation of SARS-CoV-2

infection was seen for only 3 of the cases, and this limits a cause-effect association. Larger future studies with robust correlations between pathological, clinical, and imaging data of COVID-19-associated SAT, as well as molecular and microbiological confirmation of the virus in the thyroid tissue, are needed to further elucidate its pathophysiology and clarify this possible, intriguing association.

In conclusion, although SAT is a self-limited inflammatory condition of the thyroid gland with a usually benign course, its symptoms could be confused with those of COVID-19's worrisome progression. Knowledge of a possible association between these 2 entities is, therefore, of the utmost importance in the current epidemic scenario and could help us to achieve accurate diagnoses and proper therapy for these patients.

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