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Clinical Research Article

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Is Subacute Thyroiditis an Underestimated Manifestation of SARS-CoV-2 Infection? Insights From a Case Series

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Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SAT, subacute thyroiditis, TSH, thyrotropin.

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Abstract

Context: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 18 million people worldwide and the pandemic is still spreading. After the first case we reported, we observed 4 additional cases of subacute thyroiditis (SAT) related to SARS-CoV-2 infection.
Objectives: The objective of this work is to describe additional cases of SAT associated with SARS-CoV-2 infection to alert physicians that SAT may be a manifestation of SARS-CoV-2 infection.
Methods: We describe clinical, biochemical, and imaging features of 4 patients with SAT related to SARS-CoV-2 infection.
Results: All patients were female (age, 29-46 years). SAT developed 16 to 36 days after the resolution of coronavirus disease 2019 (COVID-19). Neck pain radiated to the jaw and palpitations were the main presenting symptoms and were associated with fever and asthenia. One patient was hospitalized because of atrial fibrillation. Thyroid function tests (available for 3 individuals) were suggestive of destructive thyroiditis, and inflammatory markers were high. At neck ultrasound the thyroid was enlarged, with diffuse and bilateral hypoechoic areas and (in 3 patients) absent vascularization at color Doppler. Symptoms disappeared a few days after commencement of treatment (prednisone in 3 patients and ibuprofen in 1). Six weeks after the onset of SAT, all patients were asymptomatic and inflammatory markers had returned to normal range. Two patients were euthyroid, whereas 2 were diagnosed with subclinical hypothyroidism.
Conclusions: SAT may be an underestimated manifestation of COVID-19. Clinicians should keep in mind the possible occurrence of SAT during and after SARS-CoV-2 infection.

Freeform/Key Words: subacute thyroiditis, coronavirus, COVID-19, SARS-CoV-2, thyroid, virus

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 18 million people worldwide and the pandemic is still spreading. After our initial description of a patient experiencing subacute thyroiditis (SAT) associated with SARS-CoV-2 infection (1), 3 additional case have been reported (2-4). After the first case,

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we observed additional cases of SAT. Four of them were associated with SARS-CoV-2 infection.

Material and Methods

Patient 1

On March 1, a 38-year-old-woman underwent oropharyngeal swab for SARS-CoV-2 because of symptoms suspected for coronavirus disease 2019 (COVID-19) (Table 1). Her swab turned out to be positive. Respiratory symptoms disappeared in a few days and 2 swabs for SARS-CoV-2 (on March 13 and March 14) were both negative. On March 17, patient developed neck pain radiating to the jaw, asthenia, and fever (38.5°C). Two additional swabs for SARS-CoV-2 (on March 21 and March 23) were both negative. On March 25, the patient was hospitalized for atrial fibrillation that was treated by cardioversion. Past medical history was unremarkable for thyroid and cardiovascular diseases and the main risk factors for atrial fibrillation (ie, hypertension, heart valve disease, heart failure, myocarditis, and familiar arrhythmia) were ruled out. Laboratory exams were suggestive of overt destructive thyrotoxicosis associated with high inflammatory markers (see Table 1). Neck ultrasound showed an enlarged thyroid gland with multiple hypoechoic areas and absent vascularization at color Doppler. SAT was diagnosed and prednisone therapy (25 mg/day) was started. Symptoms disappeared within a few days. At last evaluation (on May 10), while taking prednisone 15 mg/day, the patient was asymptomatic and thyroid function tests and inflammatory markers were in the normal range (see Table 1).

Patient 2

On March 3, a 29-year-old-woman started quarantine because of contact with 2 individuals affected by COVID-19. During quarantine, the patient showed mild rhinorrhea that disappeared within a few days. At the end of quarantine (on March 17), a SARS-CoV-2 swab was negative. On April 2, patient developed neck pain radiating to the jaw associated with asthenia, palpitations, and sweating. Past medical history was unremarkable for thyroid diseases. Laboratory tests showed high levels of both free thyroxine and free triiodothyronine, undetectable serum levels of thyrotropin (TSH), and high inflammatory markers (see Table 1). Neck ultrasound showed multiple diffuse hypoechoic areas and low vascularization at color Doppler, while at ^{99m}technetium scintiscan, thyroid uptake was absent. SAT was diagnosed and, on April 15, treatment with prednisone (25 mg/day) and propranolol (40 mg/day) was started. Neck pain and fever disappeared within 3 days and the other symptoms within 2 weeks. At last evaluation (on May 18), while taking 15 mg/day of prednisone, the patient was asymptomatic, inflammatory markers were in the normal range, whereas thyroid function tests was consistent with subclinical hypothyroidism (see Table 1). Moreover, immunoglobulin M (IgM) to SARS-CoV-2 turned out to be negative whereas IgGs were highly positive.

Patient 3

On March 17, a 29-year-old-woman showed symptoms suggestive of mild COVID-19 that lasted about 2 weeks (see Table 1). On April 22, the patient developed neck pain radiating to the jaw and right ear. Past medical history was remarkable for a small, nontoxic diffuse goiter. On April 24, she experienced palpitations, tachycardia, and sweating and, given the worsening of neck pain, she started therapy with ibuprofen (600 mg/day). At the same time, neck ultrasound revealed a diffuse enlarged gland, with multiple hypoechoic areas and absent vascularization at color Doppler. Symptoms disappeared within 2 weeks. On May 7, an IgM test for SARS-CoV-2 was borderline, whereas the IgG test was frankly positive. The next day, she underwent a SARS-CoV-2 swab, which was negative. At last evaluation (on June 10), the patient was asymptomatic and inflammatory markers were in the normal range. Thyroid function tests were consistent with subclinical hypothyroidism, and the patient was started with a low dose of levothyroxine (see Table 1).

Patient 4

On April 3, a 46-year-old-woman underwent oropharyngeal swab for SARS-CoV-2 because her husband had been hospitalized for COVID-19. Her swab was positive and she developed symptoms of mild COVID-19 that lasted about 2 weeks (see Table 1). Although symptoms of COVID-19 had disappeared, 2 additional swabs were positive (on April 26 and April 28). On May 2, she developed severe neck pain radiating to the jaw, fever, palpitations, and anxiety that worsened in the following days. On May 2 and 4 she underwent 2 additional SARS-CoV-2 swabs that were both negative. Her past medical history was unremarkable for thyroid diseases. Thyroid function tests were consistent with destructive thyrotoxicosis while inflammatory markers were high (see Table 1). Moreover, an enlarged thyroid with multiple hypoechoic areas was detected at neck ultrasound. SAT was diagnosed and the patient was started with prednisone (25 mg/day). Neck pain and fever disappeared within a few days and other symptoms within 2 weeks. At the last evaluation (on June 15), while taking 20 mg/day of prednisone, the patient was asymptomatic

Table 1. Patient clinical, biochemical, and imaging features

	Thyroid features before COVID-19	COVID-19 symptoms	Time from COVID-19 SAT to onset, d	SAT symptoms	Evidence of destructive thyrotoxicosis	Inflammatory markers	Imaging	Treatment	Outcome at week 6[a]
Patient 1 Female, 38 y	July 2019 FT4 12.3 pmol/L TSH 2.7 mIU/mL	Fever (37.5°C) Rhinorrhea Anosmia Asthenia Duration: 4 d	16	Neck pain Fever (38.5°C) Palpitations Asthenia Anorexia	FT4 29.3 pmol/L FT3 8.0 pmol/L TSH 0.1 mIU/mL Tg 75.3 µg/L TgAb < 30 IU/mL TPOAb < 10 IU/mL TRAb < 1.5 IU/mL	ESR 74 mm/h CRP 11.2 mg/L	Neck ultrasound: increased thyroid volume (20 mL) with bilateral diffuse hypoechoic areas and absent vascularization at color Doppler ultrasonography	Prednisone	Asymptomatic Laboratory tests FT4 21.3 pmol/L FT3 4.9 pmol/L TSH 0.42 mIU/mL ESR 11 mm/h CRP 0.7 mg/L
Patient 2 Female, 29 y	March 2019 FT4 14.2 pmol/L TSH 0.8 mIU/mL	Rhinorrhea Duration: 3 d	30	Neck pain Fever (37.2°C) Palpitations Asthenia Sweating	FT4 31.8 pmol/L FT3 8.9 pmol/L TSH < 0.01 mIU/mL Tg 80 µg/L TgAb 38 IU/mL TPOAb < 10 IU/mL TRAb < 1.5 IU/mL	ESR 110 mm/h CRP 7.9 mg/L	Neck ultrasound: increased thyroid volume (22 mL) with bilateral diffuse hypoechoic areas and absent vascularization at color Doppler ultrasonography Thyroid scintiscan: absent uptake	Prednisone	Asymptomatic Laboratory tests FT4 13.2 pmol/L FT3 4.4 pmol/L TSH 5.9 mIU/mL ESR 4 mm/h CRP 0.1 mg/L
Patient 3 Female, 29 y	February 2019 FT4 9.8 pmol/L FT3 3.4 pmol/L TSH 1.1 mIU/mL TgAb < 30 IU/mL Neck ultrasound: increased thyroid volume (18 mL) without nodules	Fever (38.0°C) Cough Rhinorrhea Anosmia Diarrhea Duration: 14 d	36	Neck pain Palpitations Sweating	NA	NA	Neck ultrasound: increased thyroid volume (25 mL) with bilateral diffuse hypoechoic areas	Ibuprofen	Asymptomatic Laboratory tests FT4 11.2 pmol/L FT3 5.3 pmol/L TSH 8.14 mIU/mL ESR 12 mm/h CRP 0.12 mg/L
Patient 4 Female, 46 y	December 2018 FT4 11.7 pmol/L TSH 3.3 mIU/mL	Fever (38.2°C) Cough Rhinorrhea Anosmia Asthenia Duration: 6 d	20	Neck pain Fever (37.2°C) Palpitations Asthenia Insomnia Anxiety Weight loss	FT4 27.8 pmol/L FT3 6.9 pmol/L TSH < 0.01 mIU/mL TRAb < 1.5 IU/mL	CRP 8 mg/L	Neck ultrasound: increased thyroid volume (18 mL) with bilateral diffuse hypoechoic areas and absent to mild vascularization at color Doppler ultrasonography	Prednisone	Asymptomatic Laboratory tests FT4 12.6 pmol/L FT3 4.1 pmol/L TSH 4.27 mIU/mL ESR 15 mm/h CRP 1.5 mg/L

Normal ranges: FT4 6 to 16 pmol/L; FT3 2.3 to 4.2 pmol/L; TSH 0.4 to 4.5 mIU/mL; Tg < 35 µg/L; TgAb < 30 IU/mL; TPOAb < 10 IU/mL; TRAb < 1.5 IU/mL; ESR < 15 mm/h; CRP < 1.5 mg/L.

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NA, not available; FT4, free thyroxine; FT3, free 3,5,3′-triiodothyronine; SAT, subacute thyroiditis; Tg, thyroglobulin; TgAb, thyroglobulin antibodies; TPOAb, thyroperoxidase antibodies; TRAb, TSH receptor antibodies; TSH, thyrotropin.

[a]From the onset of SAT symptoms.

and both inflammatory markers and thyroid function test were unremarkable (see Table 1).

Results

After the initial case of SAT related to SARS-CoV-2 infection (1), 10 patients with SAT were referred to us. Of these, 6 lacked evidence of SARS-CoV-2 infection. We describe herein the 4 patients who had a positive SARS-CoV-2 nasopharyngeal swab or positive high-sensitive serological test for SARS-CoV-2 (see Table 1).

The patients were all women ranging in age from 29 to 46 years. They had all experienced a mild course of COVID-19. While patient 3 had previously been diagnosed with a small, diffuse nontoxic goiter, in the remaining 3 patients past medical history was unremarkable for thyroid diseases.

In all patients SAT ensued after COVID-19 symptoms had disappeared, with a lag of 16 to 36 days (see Table 1). Neck pain radiating to the jaw and palpitations were the presenting symptoms in all patients, while 3 patients reported fever and asthenia. One to two patients experienced anorexia, insomnia, sweating, and weight loss (see Table 1). One patient was hospitalized for atrial fibrillation and underwent cardioversion. Laboratory exams during the acute phase of SAT, available for 3 patients, were typical of destructive thyroiditis: thyroid hormones, and particularly free thyroxine, were increased, TSH was low to undetectable, serum thyroglobulin was high, and TSH receptor antibodies were undetectable (see Table 1). As typical of SAT, inflammatory markers were high in the 3 patients who were tested for them (see Table 1).

At neck ultrasound (performed in all patients) the thyroid was enlarged, with diffuse and bilateral hypoechoic areas. At color Doppler ultrasonography (performed in 3 patients) thyroid vascularization was absent. One patient had a thyroid scintiscan with ^{99m}technetium, which showed absent uptake, as typical of the destructive phase of SAT.

Symptoms subsided in all patients a few days after they commenced treatment (prednisone 25 mg/day in 3 patients and nonsteroidal anti-inflammatory drug in 1). Six weeks after the onset of SAT symptoms, inflammatory markers had returned to normal range in all patients. Two patients were euthyroid and 2 were diagnosed with subclinical hypothyroidism. No patient experienced a relapse of COVID-19.

Discussion

SAT is a self-limited inflammatory disease of viral or postviral origin, characterized by general symptoms, neck pain, and thyroid dysfunction, which is not usually followed by autoimmune sequelae (5-7). Although a direct correlation with viral diseases has seldom been demonstrated, the viral etiology is supported by the onset of SAT after an upper respiratory infection and its occurrence during viral outbreaks (8).

Clinical, biochemical, and imaging features were suggestive of SAT in all patients in the present series. Evidence of a close association between SARS-CoV-2 disease and SAT in 4 of 10 patients, despite an estimated SARS-CoV-2 exposure of less than 1% in the Italian population (9), strongly supports the view that SARS-CoV-2 may be considered accountable for the onset of SAT. After our first report (1), 3 additional isolated cases of SAT related to SARS-CoV-2 were described, 2 occurring simultaneously with COVID-19 (2, 3) and one 6 weeks after the onset of COVID-19 (4). Moreover, another study has reported a high rate of "subacute-like" destructive thyroiditis among patients hospitalized for severe COVID-19 (10). In the present series, as well as in our previous report (1), patients experienced SAT after the resolution of distinctive symptoms of SARS-CoV-2 infection. Therefore it may be hypothesized that SAT can ensue as either a viral or postviral manifestation of SARS-CoV-2 infection. Interestingly, thyroid involvement during COVID-19 is supported by the recent report that the virus receptor (angiotensin-converting enzyme 2) is highly expressed in the thyroid gland (11).

One patient herein reported experienced atrial fibrillation, a rather infrequent complication of SAT thyrotoxicosis, especially in a young woman. Some studies have recently described a high incidence of arrythmias among COVID-19 patients, although this complication appeared related to the cytokine storm typical of the severe course of COVID-19 (12). In our case, the medical history was unremarkable for cardiological disease and COVID-19 course was mild. It might be conceivable that both COVID-19 and SAT thyrotoxicosis have contributed to the onset of atrial fibrillation.

The clinical course of SAT is usually mild and self-limited and treatment with steroids or a nonsteroidal anti-inflammatory drug is not universally recommended (13). Interim guidance from the World Health Organization on clinical management of COVID-19 infection advises against the use of corticosteroids unless indicated for another reason (14). It is worth noting that all patients herein reported experienced severe discomfort. In addition, it is conceivable that thyrotoxicosis might negatively affect the COVID-19 course. We therefore decided that the benefit of a low-dose regimen of steroid treatment would overcome the potential risk of negative outcomes in our patients. Reassuringly, no patient developed signs or symptoms suggestive of COVID-19 relapse during follow-up.

In conclusion, our findings highlight that SAT may be an underestimated manifestation of COVID-19. Clinicians should keep in mind the possible occurrence of SAT during and after SARS-CoV-2 infection.

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Additional Information

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Disclosure Summary:

Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in the References.

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