

Is subacute thyroiditis an underestimated manifestation of SARS-CoV-2 infection?

Insights from a case series

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Conflict of interest

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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 SAT related to SARS-CoV-2 infection.

Objectives. To describe additional cases of SAT associated with SARS-CoV-2 infection in order to alert physicians that SAT may be a manifestation of SARS-CoV-2 infection.

Methods. We describe clinical, biochemical and imaging features of the 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 in three subjects) 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 three patients) absent vascularization at color doppler. Symptoms disappeared a few days after commencement of treatment (prednisone in three patients and ibuprofen in one). Six weeks after the onset of SAT all patients were asymptomatic and inflammatory markers had turned back to the normal range. Two patients were euthyroid while two 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.

Introduction

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), three additional cases have been reported (2–4). After the first case, we observed additional cases of SAT. Four of them were associated with SARS-CoV-2 infection.

Material and methods

Patient 1

On March 1st, a 38 year-old-woman underwent oropharyngeal swab for SARS-CoV-2 because of symptoms suspected for COVID-19 (Table 1). Her swab turned out positive. Respiratory symptoms disappeared in a few days and two swabs for SARS-CoV-2 (on March 13rd and on March 14th) turned out both negative. On March 17th, patient developed neck pain radiated to the jaw, asthenia and fever (38.5 °C). Two additional swabs for SARS-CoV-2 (on March 21st, and on March 23rd) were both negative. On March 25th, the patient was hospitalized because of 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 (i.e. hypertension, heart valve disease, heart failure, myocarditis and familiar arrhythmia) were ruled out. Laboratory exams was suggestive of overt destructive thyrotoxicosis associated with high inflammatory markers (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/d) was started. Symptoms disappeared within a few days. At last evaluation (on May 10th), while taking prednisone 15 mg/d, patient was asymptomatic and thyroid function tests and inflammatory markers were in the normal range (Table 1).

Patient 2

On March 3rd, a 29 year-old-woman started quarantine because of contact with two subjects affected by COVID-19. During quarantine, the patient showed mild rhinorrhea that disappeared within a few days. At the end of quarantine (on March 17th), a SARS-CoV-2 swab was negative. On April 2nd, patient developed neck pain radiated 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 (FT4) and free triiodothyronine (FT3), undetectable serum levels of thyroid-stimulating hormone (TSH) and high inflammatory markers (Table 1). Neck ultrasound showed multiple diffuse hypoechoic areas and low vascularization at color doppler, while at

^{99m}Tc scintiscan, thyroid uptake was absent. SAT was diagnosed and, on April 15th, treatment with prednisone (25 mg/d) and propranolol (40 mg/d) was started. Neck pain and fever disappeared within three days and the other symptoms within two weeks. At last evaluation (on May 18th), while taking 15 mg/d of prednisone, patient was asymptomatic, inflammatory markers were in the normal range, whereas thyroid function tests were consistent with subclinical hypothyroidism (Table 1). Moreover, IgM to SARS-CoV-2 turned out negative while IgG highly positive.

Patient 3

On March 17th, a 29 year-old-woman showed symptoms suggestive of mild COVID-19 that lasted about two weeks (Table 1). On April 22nd, patient developed neck pain radiated to the jaw and to right ear. Past medical history was remarkable for a small non-toxic diffuse goiter. On April 24th, she experienced palpitations, tachycardia and sweating and, given the worsening of neck pain, she started therapy with ibuprofen (600 mg/d). At same time, neck ultrasound revealed a diffuse enlarged gland, with multiple hypoechoic areas and absent vascularization at color doppler. Symptoms disappeared within two weeks. On May 7th, IgM test for SARS-CoV-2 was borderline, whereas IgG test frankly positive. The next day, she underwent SARS-CoV-2 swab, which turned out negative. At last evaluation (on June 10th), 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 (Table 1).

Patient 4

On April 3rd, a 46 year-old-woman underwent oropharyngeal swab for SARS-CoV-2 because her husband had been hospitalized for COVID-19. Her swab resulted positive and she developed symptoms of mild COVID-19 that lasted about two weeks (Table 1). Although symptoms of COVID-19 had disappeared, two additional swabs turned out positive (on April 26th and on April 28th). On May 2nd, she developed severe neck pain radiated to the jaw, fever, palpitations, anxiety that worsened in the following days. On May 2nd and May 4th she underwent two 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 (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/d). Neck pain and fever disappeared within a few days and other symptoms within two weeks. At the last evaluation (on June 15th), while taking 20 mg/d of prednisone, patient was asymptomatic and both inflammatory markers and thyroid function test were unremarkable (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 positive SARS-CoV-2 nasopharyngeal swab or positive high-sensitive serological test for SARS-CoV-2 (Table 1).

Patients were all females, age range 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 non-toxic goiter, in the remaining three patients past medical history was unremarkable for thyroid diseases.

In all patients SAT ensued after COVID-19 symptoms had disappeared, with a lag of 16-36 days (Table 1). Neck pain radiated to the jaw and palpitations were the presenting symptoms in all patients, while three patients reported fever and asthenia. One to two patients experienced anorexia, insomnia, sweating and weight-loss (Table 1). One patient was hospitalized because of atrial fibrillation and underwent electric cardioversion. Laboratory exams during the acute phase of SAT, available in three patients, were typical of destructive thyroiditis: thyroid hormones, and particularly free thyroxine, were increased, thyroid stimulating hormone (TSH) was low to undetectable, serum thyroglobulin was high and TSH receptor antibodies were undetectable (Table 1). As typical of SAT, inflammatory markers were high in the three patients that were tested for them (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 three 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/d in three patients and non-steroidal anti-inflammatory drug in one). Six weeks after the onset of SAT symptoms, inflammatory markers had turned to normal range in all patients. Two patients were euthyroid and two were diagnosed with subclinical hypothyroidism. No patient experienced a relapse of COVID-19.

Discussion

SAT is a self-limited inflammatory disease of viral or post-viral 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 of the current series. Evidence of a close association between SARS-CoV-2 disease and SAT in 4/10 patients, despite an estimated SARS-CoV-2 exposure of < 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), three additional isolated cases of SAT related to SARS-CoV-2 were described, two occurring simultaneously with COVID-19 (2,3) and one six weeks after the symptoms of COVID-19 had disappeared (4). Moreover, another study have 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 both a viral or post-viral manifestation of SARS-CoV-2 infection. Interestingly enough, thyroid involvement during COVID-19 is supported by the recent report that the virus receptor (angiotensin-converting enzyme 2, ACE2) 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 arrhythmias 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 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 non-steroidal anti-inflammatory drug is not universally recommended (13). Interim guidance from World Health Organization (WHO) 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 impact on COVID-19 course. We therefore decided that benefit of a low dose regimen of steroid treatment would overcome the potential risks of negative outcomes in our patients. Reassuring enough, 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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Compliance with ethical standards

Conflict of interest

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Informed consent

Written informed consent was obtained from the patients for publication of this study.

Contributorship statement

All authors discussed the results of the study. Alessandro Brancatella, Ferruccio Santini and Francesco Latrofa wrote the manuscript.

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Table 1: Clinical, biochemical and imaging features of the patients

	Thyroid features before COVID-19	COVID-19 symptoms	Time from COVID-19 to SAT onset	SAT symptoms	Evidence of destructive thyrotoxicosis	Inflammatory markers	
Patient 1 Female, 38 years	July 2019: FT4 12.3 nmol/L TSH 2.7 mIU/mL	Fever (37.5 °C) Rhinorrhea Anosmia Asthenia Duration: 4 days	16 days	Neck pain Fever (38.5°C) Palpitations Asthenia Anorexia	FT4 29.3 nmol/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 ultra bilateral c at color d
Patient 2 Female, 29 years	March 2019: FT4 14.2 nmol/L TSH 0.8 mIU/mL	Rhinorrhea Duration: 3 days	30 days	Neck pain Fever (37.2°C) Palpitations Asthenia Sweating	FT4 31.8 nmol/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 ultra bilateral c at color d Thyroid s
Patient 3 Female, 29 years	February 2019: FT4 9.8 nmol/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 days	36 days	Neck pain Palpitations Sweating	N.A.	N.A.	Neck ultra bilateral c

Patient 4	December 2018: FT4 11.7 nmol/L TSH 3.3 mIU/mL	Fever (38.2 °C) Cough Rhinorrhea Anosmia Asthenia Duration: 6 days	20 days	Neck pain Fever (37.2 °C) Palpitations Asthenia Insomnia Anxiety Weight loss	FT4 27.8 nmol/L FT3 6.9 pmol/L TSH < 0.01 mIU/mL TRAb < 1.5 IU/mL	CRP 8 mg/L	Neck ultra bilateral c vasculariz
Female, 46 years							

*From the onset of SAT symptoms;

COVID-19=coronavirus disease 2019; SAT=subacute thyroiditis; FT4= free thyroxine; FT3= free triiodothyronine; TSH= Thyroid-stimulating hormone; TgAb= thyroglobulin antibodies; TPOAb= thyroperoxidase antibodies; TRAb=TSH receptor antibodies; Tg= thyroglobulin;

ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; N.A.= not available.

Normal ranges: FT4 6-16 nmol/L; FT3 2.3-4.2 pmol/L; TSH 0.4-4.5 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.

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