A 33-year-old man with COVID-19 presented with subacute thyroiditis: A rare case report and literature review

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Abstract

We report the first case of the novel coronavirus disease 2019 (COVID-19) presenting with subacute thyroiditis in Ghaemshar, Mazandaran Province, Iran. In our patient, with the initiation of corticosteroid therapy, the symptoms of subacute thyroiditis gradually disappeared with a slow increase in thyroid-stimulating hormone (TSH) and the gradual elimination of thyrotoxicosis. This case shows that decreased TSH and persistent thyrotoxicosis may make the patient's condition worse. Managing this complication can take several weeks and can be complicated.

Keywords: Coronavirus disease 2019, corticosteroid therapy, infection, subacute thyroiditis, thyroid-stimulating hormone
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Introduction

In December 2019, a previously unknown pneumonia was reported in Wuhan, China, caused by the coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) [1,2]. The disease is highly contagious, with the pandemic reported in the 51st World Health Organization Status Report on 11 March 2020. Now named coronavirus disease 2019 (COVID-19), it presents a wide range of symptoms but until now [3], reports of subacute thyroiditis (SAT) patients with COVID-19 are limited [4]. Here, we report the first confirmed case of COVID-19 presented with SAT in Ghaemshahr, Mazandaran Province, Iran; the patient, who was admitted to our clinic, ultimately achieved remission and was discharged. The aim of this case report is to improve comprehension of the disease for clinicians, with a specific emphasis on SAT in COVID-19 patients.

Case report

A 33-year-old man presented to the clinic with fever (38.5°C), sore throat, body aches and lethargy for 2 days on 25 September 2020. Throat examination and lung auscultation were normal. Initial laboratory tests on admission to the clinic showed an elevated white blood cell count (2335 × 10^9/L), high C-reactive protein level (CRP) (46 mg/L; normal <10 mg/L), normal haemoglobin level (14.1 g/dL) and thrombocytopenia (142 × 10^3/μL). Because of the clinical features and the COVID-19 pandemic, a nasopharyngeal swab was used for sampling, and SARS-CoV-2 nucleic acid was detected by RT-PCR test; acetaminophen, naproxen and diphenhydramine were prescribed. On the sixth day, he presented to the Emergency Room with fever (39°C) and chills, sweating, sore throat and dry cough. Except for the heart rate (over 100 beats per min (bpm)), all other vital signs were in the normal range. Electrocardiogram revealed sinus tachycardia. After admission, a lung CT scan showed bilateral peripheral ground-glass opacification (Fig. 1).

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Due to ground-glass opacification and clinical symptoms, nasopharyngeal swabs were used for sampling, and SARS-CoV-2 nucleic acid was detected again by RT-PCR. By controlling the patient's fever with injected acetaminophen, heart rate decreased to 90 bpm. In laboratory tests, troponin and electrolytes were normal. Interleukin-6 and D-dimer were 11 pg/mL (normal <6 pg/mL) and 156 μg/mL (normal <1 μg/mL), respectively. Remdesivir 200 mg on the first day, followed by 100 mg daily with enoxaparin 60 mg started for 4 days. On the 8th day, the general condition of the patient improved, but he complained of a sore throat. On re-examination, we noticed a slight tenderness in the neck in the thyroid area. On thyroid ultrasound, a heterogeneous thyroid gland with bilateral ill-defined hypoechoic areas revealed SAT. No cervical lymphadenopathy was noted. His laboratory tests revealed elevated erythrocyte sedimentation rate (84 mm/h, normal <15 mm/h) and CRP (37.9 mg/L, normal <10 mg/L), but normal platelet and leucocyte counts. His thyroid function tests were thyroid-stimulating hormone (TSH) < 0.001 mUI/L, total thyroxine 23.1 μg/dL (normal range 4–11 μg/dL) and total tri-iodothyronine 236 ng/dL (normal range 75–195 ng/dL) (Table 1). Thyroperoxidase antibody and thyrotropin receptor antibody were negative (Table 1). In blood culture, after 48 hours of incubation, bacterial culture was negative. Autoimmune thyroiditis, Graves' disease and infectious thyroiditis were ruled out because of negative results for thyrotropin receptor antibody and thyroperoxidase antibody as well as the lack of bacterial growth in blood cultures after 48 hours of incubation. Eventually, given the recent COVID-19 infection, it was suspected that the SAT was caused by COVID-19. The patient was treated with dexamethasone 4 mg every 8 hours for 5 days. He was discharged with oral prednisone 25 mg daily with taper prescribed. Patient follow up was performed 10 days, 1 month and 45 days later with thyroid function tests (Table 1).

Discussion

Subacute thyroiditis is a self-limiting thyroid disorder associated with a three-stage clinical course of an initial thyrotoxic phase, hypothyroidism and return to normal thyroid function within 3 months [5]. This complication is one of the uncommon causes of thyrotoxicosis and is characterized by a painful tenderness in the thyroid gland with referred pain to the ear along with symptoms such as fever, lethargy and anorexia [6]. The exact cause of SAT is not known, but several viruses (such as influenza virus, Epstein–Barr virus, hepatitis E virus, cytomegalovirus, mumps virus, human immunodeficiency virus and chickenpox virus) have been conjectured to stimulate SAT through inducing direct or indirect damage through the circulation of the viral genome or virus-specific antibodies [7]. It seems that SARS-CoV-2 can cause SAT [8]. In the cases we examined, patients with COVID-19 developed SAT after partial recovery (Table 2) [4,9–13]. The minimum and maximum intervals from the onset of COVID-19 symptoms to the onset of SAT symptoms is 4 days [11] to 30 days [10] (Table 2). Also, the minimum and maximum intervals between the onset of SAT symptoms and SAT recovery are 4 weeks [11] to 10 weeks [4,12] (Table 2). In our case, the interval between the onset of the first symptoms of COVID-19 and the onset of SAT symptoms and the interval between the onset of SAT symptoms and recovery were 10 days and 7 weeks, respectively (Table 2).

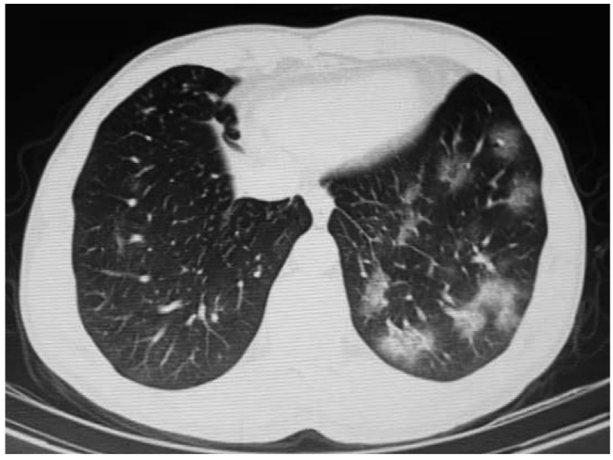

FIG. 1. Chest CT showed bilateral peripheral ground-glass opacification.

TABLE 1. **Thyroid function tests at multiple time-points during the patient's illness**

Laboratory tests (normal ranges)	Dates of thyroid function tests				
	2 October 2020	6 October 2020	16 October 2020	6 November 2020	21 November 2020
TSH (0.5–5.0 mUI/L)	**<0.001**	**<0.01**	**<0.01**	**0.1**	2.5
tT4 (4–11 μg/dL)	**23.1**	**18.5**	**18.9**	**14.3**	6.6
tT3 (75–195 ng/dL)	**236**	**221**	**229**	**211**	189
Anti-TPO	Negative	Negative	Negative	Negative	Negative
TRAb	Negative	Negative	Negative	Negative	Negative

Abbreviations: anti-TPO, thyroperoxidase antibody; TRAb, thyrotropin receptor antibody; TSH, thyroid-stimulating hormone; tT3, total tri-iodothyronine; tT4, total thyroxine. Values in bold type indicate abnormal laboratory test results.

TABLE 2. **Patient clinical, biochemical and imaging features**

Case	Place	Gender	Age (years)	COVID-19 signs	Time from COVID-19 onset to SAT, day	SAT signs	TFTs upon admission	Thyroid imaging	Time from SAT onset to recovery, week	TFTs after recovery
Mehmood et al. [12]	—	Female	29	Fever (38.3° C), dyspnoea	10	anterior neck tenderness, bilateral hand tremors, odynophagia, sweating, tachycardia (130 bpm), palpable left thyroid lobe	fT4: high tT3: high TSH: low Anti-TPO: negative TRAb: negative	—	10	—
Chakraborty et al. [11]	India	Male	58	Fever (37.5° C), tachycardia (104 bpm)	4	fever (38.5°C), neck tenderness and swelling, tachycardia (116 bpm)	fT4: high fT3: high TSH: low Anti-TPO: negative TRAb: negative	Ultrasonography: diffuse swelling of the thyroid gland with hypo-echogenicity and a solitary nodule in each lobe, reduced uptake in the thyroid scan using 99m Tc Colour Doppler: increased vascularity of the thyroid gland	4	fT4: low fT3: low TSH: high Anti-TPO: negative TRAb: negative
Mattar et al. [4]	Myanmar	Male	34	Fever (37.7° C), dry cough, headache and anosmia	9	anterior neck tenderness, diffuse asymmetric goitre, tachycardia (90–120 bpm)	fT4: high fT3: high TSH: low Anti-TPO: negative TRAb: negative	Ultrasonography: enlarged thyroid gland with heterogeneous echotexture with hypo-echogenicity Colour Doppler: reduced blood flow in both lobes	10	fT4: normal fT3: – TSH: normal Anti-TPO: – TRAb: –
Brancatella et al. [13]	Italy	Female	18	Fever (37.5° C), rhinorrhoea, cough, fatigue	18	Fever (37.5°C), fatigue, palpitation, neck pain	fT4: high fT3: high TSH: low Anti-TPO: negative TRAb: negative	Ultrasonography: bilateral hypoechoic areas with low to absent vascularization	6	fT4: normal fT3: – TSH: normal Anti-TPO: – TRAb: –
Campos-Barrera [10]	Mexico	Female	37	Odynophagia, anosmia	30	Radiating neck pain	fT4: high fT3: high TSH: undetectable Anti-TPO: negative TRAb: negative	No uptake in the iodine thyroid scan	8	fT4: – fT3: – TSH: low Anti-TPO: – TRAb: –
Khatri et al. [9]	USA	Female	41	Fever, cough, coryza	14	Anterior neck pain, neck swelling, odynophagia, fever (39.5°C), tachycardia (112 bpm), irritability, headaches, bilateral hand tremors, palpitations	tT4: - tT3: - TSH: low Anti-TPO: - TRAb: -	Ultrasonography: heterogeneous thyroid gland with bilateral hypoechoic areas	9	tT4: normal tT3: – TSH: normal Anti-TPO: negative TRAb: negative
Our case	Iran	Male	33	Fever (38.5° C), myalgia, fatigue	10	Fever (39°C), sweating, dry cough, neck tenderness, tachycardia (>100 bpm)	tT4: high tT3: high TSH: low Anti-TPO: negative TRAb: negative	Ultrasonography: heterogeneous thyroid gland with bilateral ill-defined hypoechoic areas	7	tT4: normal tT3: – TSH: normal Anti-TPO: negative TRAb: negative

Abbreviations: anti-TPO, thyroperoxidase antibody; COVID-19, coronavirus disease 2019; fT3, free tri-iodothyronine; fT4, free thyroxine; TFT, thyroid function test; TRAb, thyrotropin receptor antibody; TSH, thyroid-stimulating hormone; tT3, total tri-iodothyronine; tT4, total thyroxine.

Diagnosis of this complication is usually clinical, with confirmation by laboratory tests and neck imaging. Increased erythrocyte sedimentation rate (>50 mm/h), elevated CRP, low TSH and high levels of thyroid hormones and thyroglobulin along with absent/low titres of serum thyroperoxidase and thyroglobulin antibodies confirm the diagnosis of SAT [9]. In imaging techniques, during the acute phase, in the radionuclide thyroid scan the amount of tracer uptake is usually reduced or absent, while thyroid ultrasound shows bilateral hypoechoic areas with reduced or no vascularization [13]. In our patient's ultrasound, bilateral hypoechoic areas were diagnosed. In our patient, because of negative thyrotropin receptor antibody and thyroperoxidase antibody as well as negative blood culture 48 hours after incubation, autoimmune thyroiditis, Graves' disease and infectious thyroiditis were ruled out.

The incidence of SAT is 12.1 per 100 000/year and is more prevalent in young women than men (19.1 versus 4.1 per 100 000/year, respectively) [14,15]. Although COVID-19 covers a relatively wide range of clinical manifestations [16], the occurrence of SAT is very low among patients with the disease [4]. Nearly all COVID-19 patients with SAT have been female [9,10], with the exception of four middle-aged men in recent reports (Table 2) [4,8,11].

Evidence from a previous coronavirus outbreak in 2002 demonstrated that among 61 survivors of severe acute respiratory syndrome (SARS) who had no previous endocrine disease and were studied 3 months after recovery, four patients (6.6%) were diagnosed with primary hypothyroidism [17], and thyroid lesions were found in the autopsies of people who died of SARS [18]. Given that SARS-CoV-2 and SARS-CoV are in the same family, there is a possibility that COVID-19 also has the potential to impair thyroid function [19]. It has been reported that messenger RNA encoding expression for the angiotensin-converting enzyme 2 receptor in thyroid follicular cells makes them a potential target for SARS-CoV-2 entry [20]. Moreover, the inflammatory response may cause local damage and apoptosis of thyroid cells [9].

In a single-centre prospective study, low PCR cycle threshold values of SARS-CoV-2 and CRP were independently associated with low TSH (p 0.030) and low free tri-iodothryronine (p 0.007), respectively. Furthermore, the decrease in free tri-iodothryronine was associated with an increase in COVID-19 intensity (p 0.032). In other words, patients with low free tri-iodothryronine had more adverse results than other patients [21]. A separate study illustrates that a significant number of COVID-19 patients who require intensive care develop thyrotoxicosis and decreased TSH concentrations, in line with the SAT induced by SARS-CoV-2. In our patient, with the initiation of corticosteroid therapy, the symptoms of SAT gradually disappeared with a slow increase in TSH, and the gradual elimination of thyrotoxicosis. Therefore, the diagnosis and treatment of thyroid disorders, including SAT, in patients with COVID-19, especially those in need of intensive care, should not be neglected [22]. Remdesivir is a drug previously used to treat Ebola virus infection [23,24], but in randomized clinical trials, positive results were obtained from the use of this drug in COVID-19 therapy and it has been approved for use in COVID-19 by the US Food and Drug Administration [25]. However, the use of this drug is associated with some side effects. The most common adverse effects are nausea and elevated liver transaminases, which have been reported in patients with COVID-19 and Ebola virus infection [24]. To date, no adverse effects of thyroiditis have been reported with this drug. Therefore, in our patient, the occurrence of SAT due to the use of remdesivir seems unlikely. In patients with COVID-19 who develop SAT, care should be taken in their treatment so that they do not develop hypothyroidism later, as reported in an 58-year-old Indian man (Table 2) [11].

The exact mechanism of SAT development due to COVID-19 is not known, but it can be controlled and treated using corticosteroids. Although COVID-19 presenting with SAT is a rare condition, regardless of gender, we need to be watchful about the potential complications of SAT as an important and treatable status for COVID-19 especially in patients with severe conditions.

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval and informed consent

The form is approved by the Ethics Committee in Biomedical Research of Mazandaran University of Medical Sciences. Written informed consent was obtained from the patient for the publication of this case report as well as accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

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