

# Subacute Thyroiditis – a Neglected Complication of SARS-CoV-2 Infection

## Subakutni tireoiditis – zanemarena komplikacija SARS-CoV-2 infekcije

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### Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It usually presents with mild common cold-like symptoms. However, it can lead to series of complications with some of them being fatal. One of the rare and potentially neglected manifestations of COVID-19 is subacute thyroiditis (SAT). Viral causes of SAT documented so far include several viruses, but according to the newest reports, SARS-CoV-2 should also be added to the list. The median time between COVID-19 diagnosis and the onset of SAT symptoms is reported to be 29 days. Patients mostly present with triphasic course of symptoms – thyrotoxicosis, followed by hypothyroidism and euthyroidism. Although limited number of SAT cases after SARS-CoV-2 infection are reported, physicians should consider SAT as a differential diagnosis in COVID-19 patients. The routine assessment of thyroid function in patients with clinical suspicion of SAT or with the suspicion of any other thyroid dysfunction is advised.

### Sažetak

Koronavirusna bolest 2019 (COVID-19) infektivna je bolest koju uzrokuje SARS-CoV-2 (engl. *severe acute respiratory syndrome coronavirus 2*). Uglavnom se očituje blagim simptomima nalik na običnu prehladu, ali može izazvati niz teških komplikacija, od kojih pojedine mogu biti i smrtonosne. Jedna od rijetkih i potencijalno zanemarenih manifestacija bolesti COVID-19 je subakutni tireoiditis (SAT). Do sada je dokazano nekoliko virusnih uzročnika SAT-a, no kako najnovija istraživanja upućuju, SARS-CoV-2 bi također trebao biti uvršten na taj popis. Nadalje, izvještaji ukazuju da medijan između dijagnoze COVID-19 i početka simptoma SAT-a iznosi 29 dana. Klinički se mogu razlikovati tri stadija bolesti – stadij tireotoksikoze nakon čega slijede hipotireoza te eutireoza. Unatoč ograničenom broju objavljenih slučajeva SAT-a nakon SARS-CoV-2 infekcije, liječnici bi trebali razmotriti SAT kao diferencijalnu dijagnozu kod pacijenata oboljelih od COVID-19. Tijekom praćenja i kontrole oboljelih savjetuje se i rutinska procjena funkcije štitnjače u onih pacijenata kod kojih postoji klinička sumnja na SAT ili neki drugi poremećaj u radu štitnjače.

Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that firstly appeared in December 2019 in Wuhan City, Hubei Province, China. Since then, the SARS-CoV-2 has spread all around the world and infected approximately 65 million people<sup>[1]</sup>. Currently, the most affected countries by this pandemic outbreak are USA, India and Brazil<sup>[2]</sup>. SARS-CoV-2 is an enveloped RNA beta coronavirus and the seventh known from this family of viruses to infect humans<sup>[3]</sup>. The dominant mode of transmission is respiratory and airborne, but

other routes of transmission (through conjunctiva, fecal-oral) are also suspected<sup>[4-6]</sup>. Infected patients mostly present with mild to moderate common-cold like illness. However, some of them develop more severe manifestations of the disease including respiratory, cardiovascular, hepatic, renal, neurological, gastrointestinal, endocrine and immune complications<sup>[3]</sup>. The subacute thyroiditis (SAT) is a rare and possibly neglected complication of COVID-19.

SAT is a thyroid gland disease thought to be linked to a viral infection or post-viral inflammatory reaction. Due to its self-limiting presentation, the disease

is continually missed or accidentally diagnosed. SAT is mainly preceded by an infection of the upper respiratory tract and it is characterized by anterior cervical pain, abnormalities in thyroid function and systemic symptoms such as fever, fatigue, myalgia and anorexia. Thyroid dysfunction is usually presented in three stages – thyrotoxicosis of variable duration, followed by hypothyroidism and euthyroidism as the final recovery stage<sup>[7]</sup>. The diagnosis, in addition to a standard thyroid hormones evaluation, is based on clinical presentation, physical examination, color Doppler ultrasonography and occasionally technetium-99m (Tc-99m) scintigraphy. Viral causes of SAT reported so far include mumps, adenoviruses, rubella, HIV, cytomegalovirus, hepatitis E, dengue, influenza virus and parvovirus B19, but according to the newest reports, SARS-CoV-2 should also be added to the list<sup>[7-13]</sup>. The receptor for cellular entry of the virus is angiotensin-converting enzyme 2 (ACE-2). Rotondi et al.<sup>[14]</sup> discovered that the mRNA encoding for the ACE-2 receptor is expressed in thyroid gland which is indicative for being one of the SARS-CoV-2 targets. Furthermore, one study reported that ACE-2 expression levels were the highest in small intestine, heart, kidneys and thyroid gland which indicate that this virus is able to infect other tissues besides lungs<sup>[15]</sup>. Possible pathophysiological mechanisms of SAT are direct destructive/cytopathic effect of SARS-CoV-2 or cytokine storm effect induced by overproduction of inflammatory cytokines (e.g. interleukin-6, tumor necrosis factor-alfa)<sup>[16,17]</sup>. Until 28th November 2020, there are 13 published studies of SAT in 28 patients with COVID-19 (Table 1). Median age at the time of diagnosis was 41 years and 75% of patients were females. The median interval between COVID-19 diagnosis and the onset of SAT symptoms was 29 days. Common clinical symptoms were palpitations (80%),

fever (65%), fatigue (50%) and anterior cervical pain radiating to jaw (50%). Majority of the patients reported no previous thyroid disease, two of them had positive family history but no previous thyroid dysfunction and two of them had confirmed non-toxic diffuse, i.e. nodular goiter. A study from Muller et al.<sup>[18]</sup> suggested that a previous autoimmune or non-autoimmune disease presents no risk for SARS-CoV-2 infection or COVID-19 case severity. Moreover, 86% of patients were negative for the detection of thyroid antibodies: thyroglobulin antibodies (TgAb), thyroperoxidase antibodies (TPOAb), TSH receptor antibodies (TRAb) while three of them (all females) were positive (TgAb, TgAb and TPOAb, TPOAb, respectively). Patient's laboratory findings at the time of COVID-19 diagnosis are presented in Table 2. There is a speculation that higher C-reactive protein levels may indicate systemic spread of the virus which makes thyroid gland more prone to infection<sup>[18]</sup>. Data on thyroid ultrasound (US) was available in majority of patients and it was mostly presented as heterogeneous thyroid texture/parenchyma, with bilateral diffuse hypoechoic areas and low or absent vascularity (enlarged, non-enlarged thyroid – 31% and 69%, respectively). Furthermore, eight patients underwent thyroid Tc-99m scintigraphy which showed no (5/8) or reduced uptake (3/8). The median follow-up was 40 days (range 10-70 days) and 71% of patients regained normal thyroid function within that period. However, 11% of patients presented with subclinical hypothyroidism, 11% with hypothyroidism and 7% of them with hyperthyroidism. Similar findings were reported by Muller et al.<sup>[18]</sup>, where authors observed eight recovered intensive care unit (ICU) patients during 55 days (mean value). The majority of them recovered normal thyroid function, while two had confirmed hypothyroidism.

TABLE 1. EPIDEMIOLOGICAL AND CLINICAL CHARACTERISTICS OF SUBACUTE THYROIDITIS IN PATIENTS WITH COVID-19  
TABLICA 1. EPIDEMIOLOŠKE I KLINIČKE KARAKTERISTIKE SUBAKUTNOG TIROIDITISA KOD BOLESNIKA S COVID-19

Country	No. patients	Age	Gender	Onset of symptoms after COVID-19 diagnosis (days)	Clinical symptoms	Thyroid ultrasound	Thyroid function recovery (days)	Reference
Iran	6	26, 37, 35, 41, 52, 34	4 F, 2 M	ND	Fever, palpitations, fatigue, anterior neck pain	Bilateral hypoechoic areas in thyroid gland	Normal (30)	[19]
Italy	1	18	F	18	Fever, neck pain radiating to jaw, fatigue, palpitations	Bilateral, multiple, diffuse hypoechoic areas, low to absent vascularization	Normal (40)	[9]
Italy	8*	59, 24, 70, 61, 59, 66, 78, 65	5F, 3M	ND	ND	Diffuse hypoechoic and heterogeneity (two patients); diffuse mild and focal markedly hypoechoic areas	6 normal, 2 hypothyroidism (55)	[18]

Italy	4	38, 29, 29, 46	4 F	16, 30, 36, 20	Neck pain radiating to jaw and ear, asthenia, fever, anorexia, palpitations, atrial fibrillation, sweating, insomnia, anxiety, weight loss	Increased thyroid volume with bilateral diffuse hypoechoic areas and mild to absent vascularization	2 normal, 2 subclinical hypothyroidism (42)	[20]
Italy	1	69	F	5	Palpitations, agitation, insomnia	Enlarged hypoechoic thyroid, decreased vascularity, 30 mm nodule in right lobe (peripheral vascularization)	Hyperthyroidism (20)	[21]
Italy	1	43	F	45	Anterior neck pain, fatigue, palpitations, odynophagia, anxiety, tremor, palpitation	Diffusely enlarged and hypoechoic thyroid gland	Normal (28)	[22]
Mexico	1	37	F	30	Neck pain radiating to right jaw and ear, fatigue	ND	Hyperthyroidism (30)	[10]
Philippines	1	47	F	49	Anterior neck pain radiating to jaw	Slightly enlarged right lobe, with ill-defined hypoechoic areas and normal vascularity in both lobes	Hypothyroidism (56)	[23]
Singapore	1	34	M	10	Anterior neck pain, sinus tachycardia	Enlarged thyroid gland with heterogeneous echotexture, bilateral hypoechoic areas with ill-defined margins corresponding to the hard regions palpable, reduced blood flow in both lobes	Normal (70)	[11]
Spain	1	28	F	29	Fever, neck pain radiating to jaw, sore throat/pharyngitis, palpitations, asthenia	ND	Normal (60)	[24]
Turkey	1	41	F	ND	Fever, neck pain radiating to jaw, erythematous pharyngitis/sore throat	Relative diffuse decrease of vascularity and heterogeneous parenchyma	Normal (28)	[25]
USA	1	37	M	30	Neck pain, fatigue, chills, sinus tachycardia, tremor	Diffusely heterogeneous echotexture	Subclinical hypothyroidism (40)	[13]
USA	1	41	F	14	Odynophagia, anterior neck pain and swelling radiating to the jaw, fever, chills, diaphoresis, tremor, palpitations	Heterogeneous thyroid gland with bilateral patchy ill-defined hypoechoic areas	Normal (45)	[12]

Abbreviations: \*=ICU - intensive care unit; USA - United States of America; ND=no data

TABLE 2. LABORATORY CHARACTERISTICS OF SUBACUTE THYROIDITIS IN PATIENTS WITH COVID-19

TABLICA 2. LABORATORIJSKE KARAKTERISTIKE SUBAKUTNOG TIROIDITISA KOD BOLESNIKA S COVID-19

Case	TSH (mIU/L)	FT3 (pmol/L)	FT4 (pmol/L)	Thyroid antibodies (TgAb, TPOAb, TRAb)	WBC	CRP (mg/L)	ESR (mm/h)	Reference
1	0.07	18.9	19.5	ND	12,500	28	70	[19]
2	<0.01	25.4	22.3	ND	11,700	38	56	[19]
3	0.12	19.3	24.7	ND	9,200	18	45	[19]
4	<0.01	23.7	21.9	ND	14,800	43	83	[19]
5	0.17	21.6	26.7	ND	17,600	51	76	[19]
6	0.23	18.1	18.4	ND	13,400	23	39	[19]
7	<0.04	8.7	27.2	positive TgAb	11,200	6.9	90	[9]
8*	0.28	2.9	15.3	negative	9,800	109	ND	[18]
9*	0.33	4.0	9.6	negative	5,900	10	ND	[18]
10*	0.34	3.1	18.5	negative	6,400	139	ND	[18]
11*	0.40	3.8	16.0	negative	6,000	17	ND	[18]
12*	0.40	2.3	16.6	negative	7,300	233	ND	[18]
13*	0.43	ND	22.8	negative	6,100	52	ND	[18]
14*	8.09	ND	22.8	negative	9,700	17	ND	[18]
15*	8.27	ND	9.6	positive TgAb, TPOAb	9,500	176	ND	[18]
16	0.1	8	29.3	negative	ND	11.2	74	[20]
17	<0.01	8.9	31.8	negative	ND	7.9	110	[20]
18	ND	ND	ND	ND	ND	ND	ND	[20]
19	<0.01	6.9	27.8	negative	ND	8	ND	[20]
20	0.08	8.45	31.67	negative	ND	ND	ND	[21]
21	0.006	10.8	34.63	negative	6,600	8.8	60	[22]
22	<0.01	ND	20.6	negative	ND	66	72	[10]
23	0.05	ND	2.16	negative	ND	50.9	ND	[23]
24	<0.01	13.4	41.8	negative	11,560	122	ND	[11]
25	<0.001	ND	37.5	negative	11,200	176	ND	[24]
26	<0.008	7.7	25.7	negative	15,600	101	134	[25]
27	0.01	ND	29.61	negative	6,700	14	31	[13]
28	<0.018	ND	ND	positive TPOAb	5,790	36.4	107	[12]

Abbreviations: \*=ICU - intensive care unit; TSH - thyroid stimulating hormone; FT3 - free triiodothyronine; FT4 - free thyroxine; TgAb - thyroglobulin antibodies; TPOAb - thyroperoxidase antibodies; TRAb - TSH receptor antibodies; WBC - white blood cells; CRP - C-reactive protein; ESR - erythrocyte sedimentation rate; ND=no data

### Conclusion

In summary, SAT has emerged as a rare COVID-19 complication. It presents with clinical symptoms of thyroid dysfunction such as palpitations, fever, fatigue and anterior cervical pain. Laboratory (TSH, FT3, FT4) and imaging findings (US) were useful for the confirmation of SAT. Although limited number of SAT cases after SARS-CoV-2 infection are reported so far, physicians should consider SAT as a differential diagnosis in COVID-19 patients and the routine as-

essment of thyroid function in patients with clinical suspicion of SAT or with the suspicion of any other thyroid dysfunction is advised.

### Conflict of Interest

The authors report no conflict of interest.

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