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THE ASSOCIATION OF SUBACUTE THYROIDITIS WITH VIRAL DISEASES: A COMPREHENSIVE REVIEW OF LITERATURE

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ABSTRACT

INTRODUCTION. Subacute thyroiditis (SAT), also known as de Quatrain's thyroiditis or granulomatous thyroiditis, is an inflammatory disease of the thyroid. Most of the time, it manifests in the thirties to fifties and is more common in women. SAT can have either viral or post-viral origin. Some viruses, like influenza, COVID-19, Epstein–Barr virus, cytomegalovirus, hepatitis, coxsackievirus 16, and mumps virus, have been linked to SAT development. The COVID-19 pandemic has affected people's lives all around the world and has changed our attitude toward the treatment of many diseases. It has also made us look deeper into the subject in a way that we would be able to treat this sort of disease with a newer insight.
OBJECTIVE. Regarding the importance of this issue, we decided to summarize our extensive searches from online databases, including PubMed, Google Scholar, Medline, Web of Science, and Scopus until February 2023, which we found effective in elucidating the association of subacute thyroiditis and viral diseases.
METHOD. Different online databases were searched for narrative review articles, systemic review articles, and original articles, which were published until February 2023.
RESULT. According to the included studies, we found that there is a correlation between SAT and several viruses such as Epstein-Barr virus, influenza virus, human immunodeficiency virus, cytomegalovirus, oral and cervical virus, hepatitis, dengue virus, and SARS-COV-2. The effect of each of the viral diseases mentioned in the SAT is given in the text.
CONCLUSIONS. According to the results mentioned in the text, because SAT may be challenging for early diagnosis, due to the potential of classic symptoms as well as the interference of similar clinical symptoms between thyrotoxicosis and viral reactions, the correlation between SAT and viral diseases should be considered so that we can avoid misdiagnosis and lateness.

Keywords: *subacute thyroiditis, SAT, viral diseases, COVID-19, influenza*

INTRODUCTION

Viral diseases have influenced the lives of individuals for centuries, and we have started to feel them even more in the past couple of years with their deadly widespread outbreaks. For instance, the novel COVID-19 has reached a morbidity rate of 3.4% worldwide (with approximate total cases of 280,000,000 and 5,400,000 deaths until December 24th, 2022). Viruses are associated with all living forms (eukaryotes, bacteria, and archaea). Viral genomes comprise either DNA or RNA. These unwanted and obligate intracellular parasites can cause various disorders, including subacute thyroiditis (1).

Regarding the importance of this issue, we decided to summarize our searches from online databases until February 2023, which we found effective in elucidating the association between subacute thyroiditis and viral diseases.

METHOD

Online databases like Medline, PubMed, Scopus, Google Scholar, and Web of Science were searched for narrative review articles, systemic review articles, and original articles, which were published until February 2023. Keywords which we searched in online databases were: Subacute Thyroiditis, Subacute Painful Thyroiditis, Virus Disease, Virus Infections, Viral Disease, Viral Infections, COVID-19, SARS-CoV-2, HIV (Human Immunodeficiency Virus), Ebola, Influenza, Smallpox, HPV (Human Papilloma Virus), CFS, EBV (Epstein Barr Virus), Rhinovirus, hepatitis, hand-foot-mouth, cytomegalovirus, and Herpes. All the data and articles based on their time, subject, and resourceswere classified and studied to write a review that can be useful and helpful for further studies.

RESULTS

Subacute thyroiditis. Thyroiditis is defined as thyroid inflammation. Thyroiditis can be classified into (a) Riedel's thyroiditis; (b) autoimmune thyroiditis such as Graves' disease and Hashimoto's thyroiditis; (c) acute thyroiditis (except viral infection); and (d) Subacute thyroiditis. Subacute thyroiditis (also known as viral thyroiditis, De Quervain's thyroiditis, giant cell thyroiditis, or subacute granulomatous thyroiditis) is a self-limiting inflammation in the thyroid gland which often occurs after or in conjunction with a viral infection. It is the most frequent kind of painful thyroiditis among thyroid diseases (2).

Destruction of the thyroid gland and proteolysis of thyroglobulin (Tg) are the consequences of the inflammatory process in the thyroid, which further leads to the release of triiodothyronine (T3) and thyroxine (T4) into the blood circulation. As a result, the reduction of Thyroid-stimulating hormone (TSH) disrupts the regulation of the pituitary-thyroid axis. The gland regenerates when inflammation is about to diminish, and the hormonal balance is reestablished. Each phase is two to eight weeks long (3).

There is some evidence of a relationship between SAT and viruses such as HIV, adenovirus, hepatitis E, orthomyxovirus, mumps, rubella, cytomegalovirus, and Epstein-Barr virus (4). SARS-CoV-2 has been implicated as a probable trigger for SAT in several published case series and case reports since the emergence of COVID-19. These findings imply that the virus may cause SAT during infection or afterwards (4).

SARS-CoV-2. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first discovered in Wuhan, China, in 2019 and has become a pandemic since then. The World Health Organization (WHO) described it as a public health emergency (5).

So far, several articles have pointed out the higher prevalence of SAT associated with COVID-19, sometimes even the first manifestation of COVID-19 infection was in the form of SAT (6). SARS-CoV-2 has a stronger receptor binding with angiotensin-converting enzyme 2 (ACE2) receptors than SARS-CoV-1 according to the study by Wrapp et al. (7), which may conclude why SARS-CoV-2 cases are more. SARS-CoV-2 interacts with ACE2 in other organs, leading to the possibility of extra-pulmonary transmission and multi-organ involvement, as shown by the detection of viral RNA in blood, urine, and stool samples of individuals suffering from COVID-19.

ACE2 is expressed in many endocrine organs, including the thyroid, pituitary gland, ovary, testis, adrenal gland, and pancreas (8, 9). Furthermore, research by Rotondi and coworkers showed that the thyroid is a possible target for SARS-CoV-2 because follicular cells in the thyroid express messenger RNA (mRNA), which encodes the ACE2 receptor.

SARS-CoV-2 is known to have a wide range of effects on thyroid function. Hypothyroidism (primary or central), thyrotoxicosis (painless/atypical or subacute/painful thyroiditis or Graves' disease), and non-thyroidal sickness syndrome (euthyroid sick syndrome) are all possible side effects of the virus, according to reports (10). These findings show that the effects of the virus are highly varied on the thyroid gland, and clinicians cannot predict the thyroid abnormalities well by thyroid function tests (TFTs) (4). Direct viral injury is still the most solid evidence among the various conceivable pathways.

SARS-CoV-2 must engage molecularly with TMPRSS2 and ACE2 receptors to enter human cells.

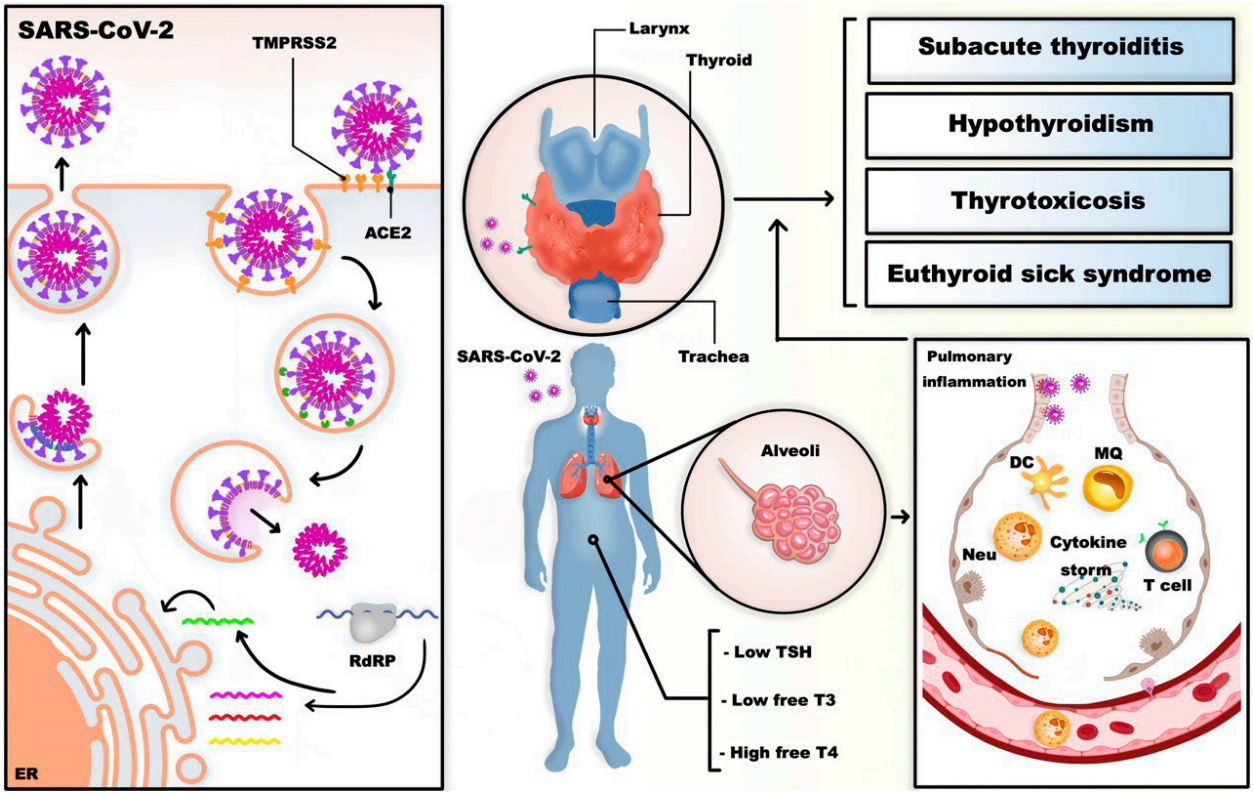

Figure 1. SARS-CoV-2 and abnormal thyroid function. SARS-CoV-2 enters target cells through interaction with Angiotensin-converting enzyme 2 (ACE2) and TMPRSS2. ACE2 is expressed in many different endocrine organs, including the thyroid; therefore, the thyroid is a possible target for SARS-CoV-2. The trachea is tightly attached to the thyroid gland. As a result, the virus may be able to enter the thyroid gland through the upper respiratory tract. COVID-19 patients showed abnormal thyroid function parameters, including low free T3, low TSH, and high free T4 concentrations. Subacute thyroiditis (SAT), hypothyroidism, thyrotoxicosis, and non-thyroidal sickness syndrome (euthyroid sick syndrome) are all possible side effects of the SARS-CoV-2.

Recent studies have showed that thyroid cells have TMPRSS2 and ACE2 mRNA (8). SARS-CoV and MERS-CoV have the same virus-receptor interaction. The thyroid has higher numbers of these receptors than other organs (heart, adipose, and small intestine) which explains why there is a relationship between subacute thyroiditis and SARS-CoV-2 (9). It is likely that this direct follicular cell damage, which causes thyroid hormone leakage, explains the override of thyrotoxic symptoms (palpitations, tachycardia, insomnia, anxiety, etc.) in more than 75% of patients and TFTs suggesting hyperthyroidism in 100% of them. Thyroid function may be harmed or impaired due to medicines used in COVID-19, such as low molecular weight heparin and glucocorticoids (11). Because not all the individuals discussed in the study by Aemaz Ur Rehman et al., received steroids and heparin to treat their COVID-19 infection, there is not enough data to back up this theory that there is definitely a connection between these drugs and thyroid dysfunction (4). The thyroid function of COVID-19 patients and healthy controls were examined in another research by Chen et al. (12).

In addition, the structural vicinity of the virus-laden upper respiratory tract to the thyroid gland may play some role. The trachea, which is infiltrated by COVID-19 virus in the course of infection is tightly attached to the thyroid gland. As a result, the virus may enter the thyroid gland through the upper respiratory tract (13). Wei et al., found that decreased T3 and T4 levels may be due to the elimination of thyroid parafollicular and follicular cells but not to the reduction in the size of thyroid follicular in an autopsy investigation of individuals infected with SARS (14).

Thyroid pathology ought to be thought of as an attainable appearance of COVID-19. Therefore, thyroid performance assessment in patients with COVID-19 could also be within the diagnostic work-up, significantly in hospitalized patients. During this cluster of patients, the low T3 syndrome prevalence is predicted to be high and is expounded to the severity of COVID-19. However, it is unclear whether T3 administration might improve prognosis in unwell patients. It ought to be thought that a concomitant administration of RDV (Remdesivir) and ATDs (Antithyroid drugs) in hospitalized patients

with thyroid gland disease might increase the chance of acute liver toxicity. Possible misinterpretation of thyroid pathology could lead to patients taking Decadron and anticoagulant medications, as these drugs can acutely alter endocrine secretion and activity (15).

COVID-19 vaccine. In general, the incidence of GD and SAT seems to be higher after COVID-19 vaccination and thyroid disorders may occur within 2 months. As reported in several case series, SAT after vaccination may result from molecular mimicry in response to viral protein exposure or abnormal immune reactivity caused by adjuvants (16).

Siolos et al., reported two women who had thyroiditis after getting a vaccine against SARS-CoV-2. The first case introduced fever and ache in the thyroid area typical of SAT, 14 days following being vaccinated with the BNT162B2 mRNA (Pfizer-BioNTech) vaccine. The other case was introduced with imaging and biochemical features consistent with silent thyroiditis, 21 days after vaccination with the ChAdOx1-S (AstraZeneca) vaccine. Both cases had no symptoms before polymerase chain reaction (PCR) test of nasopharyngeal swab and vaccination for COVID-19. SAT-associated respiratory viruses were also negative. Serological testing for mumps, measles, rubella, EBV, and cytomegalovirus (CMV) suggested immunity. Antibody titer against spike S protein of SARS-CoV-2 was measured for both cases, showing adequate antibody responses after vaccination. Sixty days after incipient evaluation, both cases were euthyroid and had no symptoms. Subacute and asymptomatic thyroiditis may infrequently happen after getting the SARS-CoV-2 vaccination. Furthermore, research is necessary to recognize the pathogenesis and prevalence of thyroid function after the COVID-19 vaccination (17).

Krupa et al., reported a male patient with SAT stimulated by SARS-CoV-2 vaccination. His throat soreness, tremor, high temperature, and weight loss of 10 pounds began seven days after receiving the second dose of the vaccine against the SARS-CoV-2. His Thyroid ultrasonography (USG) indicated expansion of the thyroid gland with a heterogeneous and hypoechoic echotexture. His test showed increasing erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and TFTs were constant with hyperthyroidism. Imaging, laboratory data and the clinical presentation demonstrated an SAT diagnosis. Nonsteroidal anti-inflammatory drugs (NSAIDs) and prednisone was started for the patient at 40 mg daily for seven days. The patient had a promising clinical response to the initiation of NSAIDs and glucocorticoid therapy and recovered (18).

Saygılı et al., reported a 38-year-old female with fatigue, swelling in the neck, loss of appetite, pain, and sweating 14 days after receiving the second dose of the COVID-19 vaccine. On the first and the 28th day, she administered the COVID-19 vaccine. She found minor pain in the thyroid after the first dose of the COVID-19 vaccine, but it finished within a few days. The patient did not have an earlier disease, preceding vaccination or drug usage. Physical examination announced stage 2 goitreand she sensed pain in the right thyroid lobe after palpation. Thyroid ultrasonography (USG) showed right thyroid lobe enlargement. SAT diagnosis was proved with thyrotoxicosis, USG findings, and a high acute phase. Propranolol and Naproxen sodium treatment was started. After treatment, the neck pain was relieved. She expressed that her problems passed away on the 14th day of the follow-up. On the 45th day, USG announced the incomplete recovery of the thyroid gland (19). The first dose of Moderna mRNA COVID-19 vaccine of a 42-year-old female was received, and she got the second dose one month later. About 5-6 days from vaccination, symptoms began. The patient suffered from right-sided and then left-sided earaches spreading to the anterior and lateral neck and lower jaw. The pain was exacerbated by coughing, swallowing, and turning her head. She had fatigue, fever, myalgia, malaise, dysphonia, dysphagia, and ear discharge. The patient did not report any history of thyroid disease or family history of neck or head cancer. Physical examination proved enlargement of the thyroid gland, which was tender after touching. On a later follow-up visit, 60 days after the biopsy, anterior neck discomfort and earache spreading to the neck that was previously described were obviated (20).

In the study by Bostan et al., found that clinical manifestations and duration of disease in SAT post-COVID-19 vaccination are often similar to classic SAT (21), but in SAT post-COVID-19 vaccination the likelihood of mild disease manifestation and better response to NSAID treatment is higher (21).

Influenza vaccine. While upper respiratory tract viruses are the most common cause of SAT, some authors claim that cases of subacute thyroiditis have been observed with both standard inactivated viral vaccines and live-attenuated vaccines (e.g., influenza vaccine), indicating that, even though thyroiditis has not been documented as a typical side effect (22). A pro-inflammatory state is generated by the individual genetic background and environmental exposure to infectious agents. A study by Hernán Martinez et al., suggested that these events in the patient may have occurred as a result of a complex interaction between the genetic background and environmental exposure. As a result of the vaccination, thyroid and bone marrow alterations occurred (23).

In a study by Momani et al., a 40-year-old male with no significant family history or personal thyroid disease was referred to a clinic suffering from enlarged thyroid on the left side coinciding with palpation to light touch and neck discomfort signs. Five weeks prior to presentation, the patient received the 2009 strain (H1N1) influenza vaccine. Two days after the vaccine injection, he developed mild fatigue, fever, and myalgia for three days. The patient started complaining of neck pain on the left side along with the anterior of the neck, shortness of breath, and palpitations nine days after the administration of the influenza vaccine. Two weeks after his neck pain presentation, the patient began to use the drug Diclofenac. Laboratory investigations showed increased CRP and ESR. Serum TSH was significantly suppressed with increased serum-free triiodothyronine (FT3) and free thyroxine (FT4). The absence of thyroid autoantibodies, clinical presentation, lack of thyroidal uptake, and ultrasound features showed SAT. Subsequently, he began to use propranolol and continued Diclofenac twice daily. Here, they document the development of SAT after influenza vaccination in an adult patient who presented with neck pain and fever. There was a main suspect that this episode of SAT was directly associated with the influenza vaccine as the episode occurred at once after influenza vaccination and in the absence of symptoms suggestive of viral infection (24).

Recurrent exposure to the vaccine, similar to the present case, as mentioned in the previous two cases, might have resulted in immune system sensitization, subsequently facilitating the development of SAT. Also, Passah et al., provided details about a case of a young woman experiencing symptomatic thyrotoxicosis and neck pain for about one month, without any past medical history of infection or sore throat. Eight weeks before symptoms occurred, she got vaccinated with a live influenza virus vaccine (25).

HIV. In a study by Chuhwak et al., a 22-year-old woman with a one-week history of low-grade fever and discomfort answered to the clinic with a deviation of her mouth to the right side and failure to close the left eye. Half-year before her symptoms, she had stomach torment with related vaginal release. On examination, she was pale, febrile, and anicteric with a low motor neuron lesion of the left facial nerve. On the assessment, this time uncovered a delicate grade-2 goitre with hyperemia of the back pharyngeal Wall. Laboratory investigation showed a positive HIV screening by double enzyme-linked immunosorbent assay (ELISA). Almost one-week history of malaise alongside the fever, pain, difficulty swallowing, and extreme delicacy over the front part of the neck showed SAT with thyrotoxicosis in HIV infection. Subsequently, the patient was replaced with a 10% dextrose infusion for 48 hours and began to use aspirin and propranolol. The delicacy in the neck proposed an intense irritation, influencing the encompassing skin and increasing temperature. A determination of sub-intense thyroiditis with thyrotoxicosis was likewise engaged because of the highlights that she created while on admission. This proposes that thyroiditis was in the horrendous stage with the arrival of putting away thyroid chemicals from the obliterated thyroid Follicles. This was upheld by the gentle rise in serum thyroxine.

In AIDS (Acquired Immune Deficiency Syndrome) patients, the chemical levels usually are lower considering the impact of non-thyroidal ailment on thyroid capacity – the purported Euthyroid wiped out disorder. It was anything but a supportive inflammation of the thyroid organ as the complete blood count (CBC) did not indicate bacterial contamination. The CBC was inside the normal range (26) (Table 1).

Dengue viral infection. The involvement of the thyroid and spinal cord in dengue patients has only been recorded in a few cases. It has been hypothesized that expanded dengue sickness may cause subacute thyroiditis. Mangaraj reported a 38-year-old woman with a dengue infection that led to complications such as subacute thyroiditis. She had fever and chills for 12 days with pain in her head, muscles, and retro-orbital. After that, throat pain, difficulty in swallowing, severe fever, and tremors appeared for two days. Also, she had tachycardia and grade 1 goiter, which was touchable and consistent. The ESR was raised; furthermore, dengue serology nonstructural one protein antigen test showed a positive result. A probability of thyrotoxicosis was established by total T3 and T4 raising and decreased quantity of TSH. Thyroid ultrasonography showed diffused hypertrophy and slight angiogenesis with heterogeneous parenchyma. Thyroid autoantibodies (antibodies to thyroid peroxidase) were negative, and thyroid scintigraphy with complete technetium99m showed a lack of absorption of the tracker in both thyroid lobes according to the diagnosis of subacute thyroiditis. Therefore, they prescribed oral beta-blocker and prednisolone, which showed a good clinical improvement by relieving the symptoms (27).

Infectious factors vary widely and may induce thyroid autoimmunity through a mechanism. Beta-blockers can help control adrenergic side effects, but antithyroid drugs had no role in the treatment of thyrotoxicosis due to thyroiditis. The underlying phase of hypothyroidism in subacute thyroiditis is typically trailed by a transient phase of hypothyroidism, after which the state of hypothyroidism recuperates. However, permanent hypothyroidism can occur if the inflammation is severe and long-lasting. All the

Table 1. Summary of the studies on the association of SAT and viral diseases

First author	Virus	Diagnosis	Time	ESR, CRP	Degree of toxicosis	Presence of pain	Outcomes
Bellastella (2022) (13)	SARS-CoV-2 Infection	Increased levels of free thyroid hormones and TSH	Few weeks after			No neck pain	Tachyarrhythmia, Ear pain, hemorrhage, necrosis, thrombosis, acute hypoadrenalism, venous thrombo-embolism
Chen (2020) (30)	Rabies Vaccination	An increase in ESR and CRP levels, doubled the amount of P-ANCA, uneven zones with lower echoes on both lobes were shown in ultrasound	After the first dose	ESR = 32 mm/h, CRP =16.9 mg/L		Pain in front of neck	High fever with a highest axillary temperature of 39.2°C, pain and swelling of the anterior neck, oral and genital ulcerations, erythema nodosum on both legs, pseudo-folliculitis on thoracodorsal areas
Chuhwak (2013) (26)	HIV	Difficulty and pain in swallowing, Thyroxine(T4): 16.0 ng/100ml, Tri-iodothyronine(T3): 1.9 ng/ml, Thyrotropin (TSH): 0.9m.i.u/ml		ESR: 130mm/hr		Neck pain	Deviation of mouth to the right side, inability to close the left eye, neck pain, palpitations, shaking of the body, coarse tremors of the hand, and swelling of the anterior aspect of the neck
Mangaraj (2021) (27)	Dengue viral infection	Complete absence of tracer uptake (normal uptake: 0.4–1.5%) in both thyroid lobes, the presence of diffuse thyroid enlargement with heterogeneous parenchyma and mild vascular enhancement in ultrasound, elevated total T3 and total T4 levels with suppressed TSH	12 days	ESR=86 mm/1st h,	Overt thyrotoxicosis	No neck pain	High-grade fever (temperature 38°C) with chills, myalgia, headache, retro-orbital pain, severe throat pain, difficulty in deglutition, limb tremors, tachycardia of 120 beats/min, grade one goiter

Chiaruzzi (2020) (29)	Erythrovirus B19 infection	High Free T3, free T4, and serum thyroglobulin levels, bilateral hypoechoic regions and a widespread relative reduction in vascularity throughout the gland, thyroid tenderness, and lack of radioactive iodine on imaging.	Three weeks			Thyroid tenderness	Sore throat, asthenia, history of fever, myalgia, thyroid tenderness, pain on joint palpation, and erythematous pharyngitis
Engkakul P (2011) (31)	Coxsackie virus	Painful thyroid enlargement, T4: 2.7 ng/dL (normal, 0.7–1.5), T3: 4.0 g/mL (normal, 1.7–3.7), TSH: 0.01 mU/L (normal, 0.4–4.9	2.5 weeks	ESR: 88 mm/h CRP: 44.7 mg/L		Neck pain	Neck pain, fever with ulcerated lesions of the oral mucosa and papulovesicular lesions at both palms and soles
Tas (2012) (32)	hepatitis B virus (HBV) infection	Hepatomegaly and subtle thyroid enlargement were shown in ultrasound	30 days	ESR=120 mm/h		Myalgia and neck pain	Myalgia, fatigue, abdominal distention, neck pain, tachycardia
Parana (2000) (33)	Antiviral combination therapy for Hepatitis C (HCV)	hyperthyroidism-like symptoms, high free T4, low TSH levels, and negative anti-TPO	Three months after therapy	ESR=35 and 45 mm/h		Neck pain	Neck pain, irritability, weight loss
Volta (2005) (34)	Epstein-Barr virus (EBV) infection	Increased levels of freeT3 and free T4, suppressed TSH, thyroid enlargement in ultrasound		ESR=115 mm/h CRP=26.2mg/l	Symptoms of thyrotoxicosis	No neck pain	Lymphadenopathy, tachycardia, leukocytosis
Daniels (2001) (35)	Viral infection or autoimmune etiologies	Hypothyroidism, low radioiodine uptake in 24 hours	Several months	ESR= 4, 28, 69 and 79 mm/h	Transient thyrotoxicosis in some patients	Painless or minimally painful	Weight loss, low thyroid pain and tenderness

ESR: erythrocyte sedimentation rate.
CRP: C-reactive protein.
P-ANCA: perinuclear anti-neutrophil cytoplasmic antibody.
TSH: thyroid-stimulating hormone
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
IL-6: Interleukin-6
FT4: Fast T4
FT3: Fast T3
The reference ranges: TSH (0.34– 4.80 mU/L), FT4(7.82–17.29 pmol/L), FT3(3.38–6.45 pmol/L) and IL-6 (<6.4 pg/mL)

patients declared the symptoms were resolved 6-10 days after the launch of the fever and (28).

Erythrovirus B19 infection. Chiaruzzi et al., described an uncommon case of Erythrovirus B19 (EVB19) related to subacute thyroiditis. A middle-aged man came to their medical department because of a sore throat, asthenia, febrile history which lasted three weeks, and myalgia. Later examinations showed thyroidtenderness, and erythematous pharyngitis. Serological analyses showed that his free T3, T4 hormone and serum thyroglobulin were high, but TSH was undetectable. Also, no antibodies against thyroglobulin and thyroperoxidase were found, and the TSH receptor was not blocked. Without any lesions, a thyroid ultrasound revealed bilateral hypoechoic regions and a widespread relative reduction in vascularity throughout the gland. The thyroid tenderness related to hyperthyroidism, the lack of radioactive iodine on imaging, and an elevated level of serum thyroglobulin all supported the idea that this person had subacute thyroiditis. This person was infected with EVB19, which was confirmed by PCR. When T-cells recognize viral and cell antigens, thyroid injury may occur. Infected host cells undergo an apoptotic process that leads to cell death in 48 hours, probably due to the production of the non-structural protein NS1. This suggests that the EVB19 virus has a cytopathic impact. Erythrovirus B19 is a non-enveloped deoxyribonucleic acid virus linked to autoimmune thyroid illnesses such as Graves' disease alongside Hashimoto's thyroiditis in the past (29).

Rabies vaccination. Chen et al., reported a 26-year-old woman with SAT and Behçet's disease diagnosis after a dog biting and rabies vaccination. The Laboratory information showed significant leukocytosis, an increase in ESR as well as CRP and doubled amount of perinuclear anti-neutrophil cytoplasmic antibody (P-ANCA) without specific antibody increment. A thyroid ultrasound indicated uneven zones with lower echoes on both lobes. Behçet's disease and SAT were intended in the local hospital, and after that, her P-ANCA tripled, and the thyroidstimulating hormone mildly increased. However, she had standard free thyroxines, ESR, and CRP. Furthermore, hypo-echoic parts decreased in the thyroid ultrasound experiment 10 weeks later. This patient was the first reported case of vaccination-triggered SAT as an adverse effect (30).

Hand-foot-mouth disease. Childhood de Quervain thyroiditis related to hand–foot–mouth disease from coxsackie infection was reported in a 2.7–year–old boy. At first, he had a brief thyrotoxic phase followed by euthyroidism and a transient hypothyroid phase. Prednisolone was prescribed for him, and after two months, the symptoms were relieved (31).

Hepatitis virus. Tas et al., reported a 52-year-old female with a 5-day history of pain in the neck, fatigue, myalgias, and abdominal distention. Ultrasonography showed hepatosteatosis and hepatomegaly. Ultrasound of the thyroid gland revealed a subtle gland enlargement. The diagnosis indicated subacute thyroiditis induced by hepatitis B virus (HBV). Beta-blocker (propranolol 60 mg/day, orally) was prescribed for the patient. After six months, thyroid function and inflammatory markers were back to normal (32).

Parana et al., had three Hepatitis C (HCV) patients with episodes of subacute thyroiditis during treatment with antiviral combination therapy. All patients showed hyperthyroidism-like symptoms, which could be misdiagnosed as IFN complications. And with continued antiviral therapy, thyroid function elevated progressively alongside hyperthyroidism treatment. The result showed that subacute thyroiditis could result from combination antiviral therapy, and it is better to be evaluated in patients with compatible symptoms to be differentiated from IFN complications (33).

Epstein-Barr virus (EBV). One of the causes of thyroid dysfunction is Epstein-Barr virus. Volta et al., described a 3-year-old girl with unknown-origin fever resistant to antibiotics. There was an unexplained tachycardia with unexpected results in thyroid functions. As a result, thyroid function was investigated. Increased levels of FT3 and FT4 suppressed TSH. Also, PCR showed EBV DNA presence in plasma and leucocytes with an elevated titer of anti-EBV IgM. These findings suggested subacute thyroiditis induced by EBV. The girl has been prescribed a 10-day course ofsteroids (deflazacort, 1.5 mg/kg per day, orally, once daily) which showed a progressive resolution of spleen and liver enlargement, lymphadenopathy, and fever. After three months, her thyroid function returned to normal (34).

Others. In a study published in 2001, nine patients with subacute thyroiditis were included, and six had a history of viral disease. None of them had autoimmune thyroid disease in their relatives, and eight patients tested negative for thyroid peroxidase antibodies. One of the most prevalent types of thyroiditis is painful subacute (granulomatous) thyroiditis. Commonly, the painful type of thyroiditis is followed by a viral disease related to bilateral or unilateral soreness. In individuals with destructive thyroiditis, the absence or presence of pain is often regarded as a principal diagnostic point. Painful thyroiditis is both self-limiting and post-viral, while painless thyroiditis is usually autoimmune and requires lifelong monitoring. But evidence suggests that some people with painless thyroiditis had a viral origin and that few patients with painful thyroiditis had autoimmune aetiology. After hepatitis C immunotherapy, lymphocytic subacute

thyroiditis is prevalent; however, painful subacute thyroiditis is uncommon (35).

Treatment. Once the diagnosis is determined, initiating the treatment is necessary; however, there is no consensus on the steroid implementation scheme. The implementation scheme in Domin et al., department is as follows: prednisolone (40 mg daily) with a gradually decreasing procedure with weekly dose reduction for 6-8 weeks. In less severe cases or subjects with contradictory orders of steroids, using NSAIDs such as ibuprofen or naproxen can be effective; however, it is not mandatory (36). Considering the study by Sato et al., the effectiveness of stand-alone steroid treatment is preferable to NSAIDs (37). As a supplemental treatment, in the hyperthyroidism stage, Domin et al., recommendation is propranolol and, in hypothyroidism levothyroxine but solely when the patient is symptomatic (36).

A new therapeutic approach was inquired into and reported in a study by Shao-Gang et al., injections of lidocaine and dexamethasone saline solution within the thyroid every other day for one week (38). Comparing the results of typical treatment with oral prednisolone, with the group receiving injections, those receiving injection was described to have a more rapid reduction of pain and shorter treatment duration. Unfortunately, surgical treatment will be needed for some patients, especially when a fine needle aspiration biopsy (FNAB) examination suggests malignancy or when the patient is inattentive to pharmacological treatment and has persistent symptoms (tender goiter, dysphagia) (39). Most patients will not experience complications after recovery; however, a relapse or persistent/chronic hypothyroidism may be experienced by some (36).

CONCLUSION

Thyroid lesions in COVID-19 are due to destructive or inflammatory thyroiditis secondary to cytokine storm. Also, it has been hypothesized that treatment of COVID-19, particularly low molecular weight heparin, can also affect thyroid functions and damage the gland. Routine thyroid function test in patients with severe infection phase of COVID-19 is encouraged to detect thyrotoxicosis. EVB19 infection of host cells leads to an apoptotic process, probably associated with the expression of non-structural protein NS1, resulting in cell death in 48 hours, suggesting a cytopathic impact of the EVB19 virus. Dengue infection can lead to autoimmune diseases, especially in the thyroid. SAT has been cautioned to be a complication of dengue syndrome. Antiviral combination therapy in hepatitis can leads to thyroid dysfunction. Physicians need to be conscious that SAT can result from the administration of influenza vaccines and the ones containing (H1N1) pdm09 strain and rabies inoculation.

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