



# Subacute Thyroiditis as Evidence of SARS-CoV2 Related Autoimmune Disorders and Case Descriptions

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## Abstract

**Context:** Subacute thyroiditis has been classified as an autoinflammatory condition and is mainly caused by a viral infection. According to the pathogenesis of SARS-CoV2 infection, which is mainly based on the uncontrolled inflammatory immune response, several studies have investigated the possible association between SARS-CoV2 and subacute thyroiditis. The present study aimed to review and organize the studies that have investigated the possible association between SARS-CoV2 and subacute thyroiditis.

**Evidence Acquisition:** Initially, we observed and provided evidence on the possible roles and mechanisms of SARS-CoV2 in inflammatory and autoimmune diseases, and then we discussed the findings on the association between subacute thyroiditis and SARS-CoV2 infection.

**Results:** Investigation of other autoimmune and inflammatory disorders, and previous studies on the role of viruses in the pathogenesis of subacute thyroiditis, as well as studies on the inflammatory mechanism of SARS-CoV2 infection support the hypothesis that SARS-CoV2 may initiate subacute thyroiditis.

**Conclusions:** The existing evidence suggests that subacute thyroiditis should be considered a late symptom of COVID-19.

**Keywords:** Autoimmune disease, COVID-19, Inflammation, SARS-CoV2, Subacute thyroiditis

## 1. Background

Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) has started to spread widely worldwide (2) by the disclosure of the first reports regarding the emergence of a new coronavirus responsible for lethal pneumonia in China (1). Although reports on the death rate of SARS-CoV2 infection vary in different countries, more than 20% of cases are involved with critical forms of pneumonia (3). In terms of pathogenesis, viral infection triggers a cascade of uncontrolled inflammatory immune responses that lead to the production of massive amounts of cytokines, overactivation of immune cells, and development of acute respiratory stress syndrome (ARDS) (4). These processes are expected to be a critical cause of death in patients (5). SARS-CoV2 infection appears to trigger the same inflammatory immune response that occurs in autoimmune diseases (6). Viruses are known to play a role in several immune disorders (7,8), and there is some evidence linking SARS-CoV2 to autoimmune disorders and inflammatory conditions, including subacute thyroiditis (9,10).

Subacute thyroiditis or "de Quervain's thyroiditis" is a rare autoinflammatory thyroid disorder that mainly affects middle-aged women (11,12). Although the exact mechanisms are not fully understood in terms of pathophysiology and etiological factors, subacute thyroiditis is believed to be an

autoinflammatory or autoimmune disease due to its inflammatory nature. Moreover, several studies have suggested that inflammation is triggered by viral infections (13). Some epidemiological and experimental evidence, including a higher incidence of subacute thyroiditis in viral outbreaks (14) and the presence of viral particles in the thyroid follicles of patients with subacute thyroiditis (15) underline the hypothesis that there is a strong association between viral infections and subacute thyroiditis (13,16,17).

More recently, a few cases of subacute thyroiditis were observed in SARS-CoV2 infected patients. The present study appraised the potential association of subacute thyroiditis with SARS-CoV2 by collecting evidence from other cases of autoimmune diseases and case reports on subacute thyroiditis.

## 2. Immunopathogenesis of SARS-CoV-2

SARS-CoV-2 started from Wuhan, China, in 2019 and soon spread as a pandemic worldwide (1). The disease signs range from asymptomatic to severe and include dry cough, fever, weakness or severe ARDS, and further life-threatening multi-organ compromise (18). The virus SARS-CoV2 penetrates cells through the interaction of its spike protein with the angiotensin-converting enzyme 2 (ACE2) receptor of cells (19). Several tissues express the ACE2 receptor and are theoretically prone to SARS-CoV2 infection (20,21). Upon attachment of the virus via protein S -

ACE2 interaction, the enzymatic activities in the host cells lead to the cleavage of the protein S, which in turn determines the entry of the virus into the cell (22).

In the early post-infection stages, it appears that reduction in the frequency of some innate immune cells, such as NK cells and eosinophils plays a role in the development of severe forms of COVID-19. Low numbers of circulating eosinophils and NK cells have been proposed to poor marker prognosis (18,23,24). Furthermore, in severe cases, NK cells express a higher level of inhibitory molecules and have lower cytotoxic properties (25). Despite this reduction in circulating immune cells, data from bronchoalveolar lavage investigations showed aggregation of immune cells (e.g, dendritic cells) and activated neutrophils in the respiratory tract (26). In addition, monocytes with inflammatory phenotypes increase in the peripheral blood of patients with severe COVID-19 (27).

Evidence of both MERS-CoV and SARS-CoV2 infections show that uncontrolled virus loading is correlated with delay and suppression in type I and III IFN responses (28,29). Following the delay in the IFN response, an increase in chemokines induces the migration of inflammatory monocytes, macrophages, and neutrophils (30). This aggregation and activation of innate cells are simultaneous with an increase in inflammatory cytokines, such as IL-6, IL-8, and TNF- $\alpha$  (31). In a general immunological concept, CD4 + T cells begin to activate and differentiate into lymphoid organs upon this inflammatory activation of innate cells. Upon activation, helper T cells migrate into inflamed tissue (32). In cases with complete elimination of the virus, most T cells go through the apoptosis process to save the balance of the immune system, and a small percentage of T cells called memory T cells remain to protect themselves from getting infected (33). This immunological memory is also believed to play a role in autoimmune diseases (34).

In the case of COVID-19, the results suggest that circulating T helper and Treg cells decrease in the peripheral blood of patients with severe COVID-19 (35). However, it is not clear whether this decrease is due to the migration of these cells into the inflamed tissue or is a direct effect of the virus (35). Further studies on subsets of T cells in SARS-CoV2 infected cases showed high expression of surface activation markers, such as CD38 and CD44 in both CD4 and CD8 T cells (36). It is worth mentioning that the increased frequency of CD44 positive cells has been demonstrated in association with inflammatory and autoimmune diseases (37). More detailed investigations have shown that despite the reduction of lymphocytes, particularly the Treg lymphocytes in the peripheral blood of COVID-19 patients, subgroups of inflammatory T helper, such as CCR6 + Th17 are increasing (35,38). The reduction in Tregs and an increase in Th17 cells have also been frequent in autoimmune diseases and inflammatory disorders (39,40).

In addition to the cellular immune response, SARS-CoV2 also triggers antibody-mediated responses (41). In some cases, SARS-CoV2 antibodies are detectable less than seven days after infection (42). However, in most cases, antibodies are detectable after one week (42,43). Based on the evidence, these antibodies have a neutralizing ability, suggesting their potential role in virus clearance (44,45). Despite reports on the potential benefits of neutralizing antibodies in viral clearance and protection against viruses, there are questions about the pathological roles of these antibodies. The first evidence on the appropriate harmful effects of antiviral antibodies was found in the animal models of SARS, which showed the role of anti-spike IgG protein in lung damage. This study demonstrated that anti-protein S antibodies could trigger a cascade of inflammatory events and cause aggregation of innate inflammatory cells in inflamed tissues (46). According to the high similarity between the S proteins in SARS-CoV and SARS-CoV2, this mechanism could be deliberate via a different mechanism of SARS-CoV2 in inducing tissue damage and autoimmunity (47).

### 3. SARS-CoV2 related autoimmune disorders

As previously mentioned, COVID-19 shares similar properties with autoimmune diseases. In severe cases, hyperferritinemia, fever, and uncontrolled production of inflammatory cytokines are related to mortality (48). This uncontrolled and massive production of cytokines is the so-called "cytokine storm" and is blamed for the most severe symptoms of COVID-19 (49,50). Excessive activation of resident or migrating innate immune cells in the respiratory tract and lung is thought to be responsible for the "cytokine storm" (51). Genetic factors have been shown to be strongly associated with increased cytokine production in critically ill patients (52). This cytokine storm and inflammatory environment could potentially result in the activation of self-reactive immune cells via a mechanism called bystander activation (53). In this process, nonspecific immune activation and cytokine production could lead to the activation and differentiation of auto-reactive T lymphocytes and break tolerance to autoantigens (54,55). In addition to bystander activation, molecular mimicry could be another autoimmune mechanism of SARS-CoV2 (7,56). Molecular mimicry refers to a mechanism in which similarities between viral antigens and autoantigens lead to cross-reactivity of the immune response and induction of the immune response against autoantigens (7). SARS-CoV-2 proteome analysis showed that this virus shares at least three short amino acid sequences with human proteins (57). These similarities and molecular mimicry have been proposed as potential mechanisms for autoimmune

lesions in the lung and respiratory tract (58). Furthermore, a SARS-CoV-2 5-amino acid peptide has been found to be identical to a sequence in lung surfactant proteins and may be associated with autoimmune lung damage (59).

Furthermore, investigations suggested the cross-reactivity of anti-S protein antibodies with various human proteins, including tissue thyroid peroxidase, ENA, myelin basic protein, transglutaminase 3, transglutaminase 2, mitochondria, nuclear antigen, S100B, collagen  $\alpha$ -myosin, and claudin 5 + 6 (59). In addition to the aforementioned basic evidence on the appropriate role of SARS-CoV2 in autoimmune responses, strong evidence suggests the presence of autoantibodies in COVID-19 patients\*. The higher frequency of anti-nuclear autoantibodies (ANA), lupus anti-coagulants and antibodies, and a high titer of anti-SSA / Ro antibodies have been reported in hospitalized patients with COVID-19 (60).

In another study conducted to discover the anti-phospholipid antibody profile in COVID-19 patients, it was shown that more than half of the submitted cases had a detectable level of anti-cardiolipin or anti- $\beta$ 2 glycoprotein 1 (a $\beta$ 2GP1) antibodies or both (61). These antibodies are thought to be responsible for hypercoagulation in patients with severe forms of COVID-19 (61,62). The anti-IFN antibody is another autoantibody found in these patients. It has been suggested that this neutralizing antibody is an unfavorable prognostic marker in these patients as it may suppress the antiviral response of type I IFNs (63).

The presence of the mentioned autoantibodies and other autoantibodies clearly shows the association between SARS-CoV2 and autoimmune conditions. Several autoimmune diseases have been studied to discover the role of SARS-CoV2 on their onset and progression (10,61,64,65). One of the most investigated disorders in this regard is Guillain-Barré syndrome (GBS) (66). This condition is an acute autoimmune polyradiculoneuropathy that causes pain, tingling, progressive autonomic dysfunction of the myelin sheath, and Schwann cells targeted by the immune system demyelinating polyneuropathy (67). The first evidence on the association between GBS and SARS-CoV2 was reported in a clinical study. In this study, 71-year-old men were diagnosed with GBS weeks after COVID-19 symptoms (68).

Moreover, in another study, five cases of GBS were reported to show GBS symptoms within only 5 to 10 days of COVID-19 initiation (10,65). Inflammation can also cause disturbances to the blood-brain barrier and facilitate the process (69,70). Along with GBS, other autoimmune disorders, such as Miller Fisher syndrome, systemic lupus erythematosus, Kawasaki disease, antiphospholipid syndrome, and immune thrombocytopenic purpura (ITP) have also been reported in association with SARS-CoV2 infection (64).

#### 4. Clinical significance of subacute thyroiditis

Neck pain is the most common symptom in patients with subacute thyroiditis, followed by night fever. Other symptoms, such as fatigue, muscle pain, and malaise are also reported (71). The most frequent and significant laboratory finding in patients with subacute thyroiditis is the high erythrocyte sedimentation rate (ESR), together with a high level of C-reactive protein (CRP). Elevated levels of T3 and T4 may also be found; however, the presence of serum anti-thyroid antibodies is rare (71-73). The main feature of Doppler ultrasound is the presence of hypochoic and heterogeneous areas (74).

Rapid growth similar to a malignant thyroid tumor is also observed in these patients, which could be misdiagnosed as cancer (75). Subacute thyroiditis is considered a self-limiting disease, and its symptoms may subside within weeks to months in most cases. However, in some patients, medications are needed to resolve symptoms, and the first treatment choice in this regard is nonsteroidal anti-inflammatory drugs (76). In some cases, corticosteroids, such as prednisone are prescribed as a second line of treatment (77). Despite the self-limiting nature of subacute thyroiditis and the drug's efficacy, some patients experience a relapse of symptoms (71,78).

#### 5. Viral infection responsible for subacute thyroiditis

Early reports of the association between subacute thyroiditis and infections were based on epidemiological findings (14,79), which showed a greater likelihood of developing subacute thyroiditis following upper respiratory tract infection. Symptoms of subacute thyroiditis in a large percentage of patients begin in early autumn when seasonal viruses, such as enteroviruses are prevalent (14,72,79). In addition to epidemiological studies, the experimental results also highlight the associations between subacute thyroiditis and viral infections (80). Primary reports showed that the presence of virus-like particles in the follicular epithelium of patients with subacute thyroiditis (15) and a higher frequency of anti-influenza antibodies was also demonstrated in these patients, compared to normal cases (81).

Evidence indicates that the presence of viral particles in the thyroid glands of patients with subacute thyroiditis is rare. In one study, virus-like particles were isolated from 17% of patients, in which the isolated viruses appear to be paramyxovirus or human foam virus (HFV) (82,83). However, other studies have shown no significant association between subacute thyroiditis and HFV frequency (13,84,85). The mumps virus is also suspected to be responsible for the onset of subacute thyroiditis. In addition to epidemiological

data showing a higher incidence of subacute thyroiditis during mumps outbreaks, serological data show a higher frequency of anti-mumps antibodies in patients with subacute thyroiditis (17,86). Some unusual symptoms of mumps, such as parotitis and orchitis are also significantly associated with subacute thyroiditis (86). In addition to this indirect evidence, the mumps virus has been isolated from the thyroid tissues of patients with subacute thyroiditis (17).

As mentioned previously, other viruses, such as Enterovirus, coxsackievirus, adenovirus are also believed to play a role in subacute thyroiditis (87-89). Additionally, in a case study, symptoms of subacute thyroiditis were shown to begin one month after acute rubella virus infection (90). Most of the evidence is based on the higher titer, and higher frequency of antiviral antibodies in patients with subacute thyroiditis, and viral RNA or DNA was barely found in the aspiration samples (80,91-93).

## 6. Evidence on the roles of SARS-CoV2 in subacute thyroiditis

Despite the lack of experimental data indicating the exact mechanisms in which SARS-CoV2 can affect thyroid functions and play a role in subacute thyroiditis, some direct and indirect evidence supports the potential role of SARS-CoV2 in thyroid dysfunction and subacute thyroiditis. It should be considered that thyroid tissue is one of the tissues expressing a high amount of the ACE2 receptor of SARS-CoV2 (94). Data from real-time PCR experiments showed abundant amounts of ACE2 mRNA in thyroid follicular cells (95). This could suggest the possibility of the presence of viral particles in the thyroid glands. However, there is still no experimental and direct evidence demonstrating the presence of SARS-CoV2 viral particles in the thyroid, and further studies are needed to find out whether SARS-CoV2 directly infects follicular cells through this receptor or not. In addition to this question, several studies have demonstrated impaired thyroid function in patients infected with SARS-CoV2 (96,97).

## 7. Main mechanisms of viral infection in subacute thyroiditis

Although there is a notable association between viral infections and subacute thyroiditis, the exact mechanisms of developing subacute thyroiditis in the case of a viral infection need to be studied in detail. Further evidence introduces the response of the immune system during viral infection as a potential mechanism in this regard. This evidence includes the infiltration of immune cells, particularly cytotoxic CTLs, into the thyroid follicles of patients with subacute thyroiditis (98,99). Furthermore, monocytes and macrophages that produce a huge amount of factors, such as VEGF, FGF, PDGF, and TGF

have been found to induce granulomatosis in patients' thyroid (100). An extremely associated factor is HLA-B35, which is expressed in most cases (101).

Interestingly, this HLA allele has also been reported in association with a chronic and severe form of other viral infection, such as hepatitis (102,103). Other immune-related factors, such as interleukin -1 receptor antagonist and TNF have been demonstrated in association with subacute thyroiditis (104-106). There are also other data suggesting the role of the immune system in developing subacute thyroiditis. One of these data is the increased chance of developing subacute thyroiditis following the flu vaccination (107). This suggests the dominant role of immune activation (not the virus itself) in inducing subacute thyroiditis. Another evidence is the reports on subacute thyroiditis conditions in cancer or hepatitis patients after receiving immune-activating drugs (108,109). Regarding the data provided on the importance of the immune system and its possible roles in subacute thyroiditis, it seems logical to study the immune system in investigations on the mechanisms in which viral infections lead to subacute thyroiditis.

## 8. Case reports of SARS-CoV2-related subacute thyroiditis

Case reports constitute most of the published studies on the association between subacute thyroiditis and SARS-CoV2. Here we provide the latest results of the correlation between SARS-CoV2 in the case of subacute thyroiditis. In a retrospective cohort study of thyroid function in patients with moderate and severe SARS-CoV2 infection, TSH and total T3 were decreased compared to other viral and non-viral pneumonia. Furthermore, they showed a negative correlation between serum TSH levels and symptom severity; however, the T4 level in these patients appeared to be normal (96).

In agreement with the cited data, another study conducted on 274 COVID-19 patients indicated lower levels of TSH and free T3 in infected rather than cured cases (110). In another study, it was shown that 20% of COVID-19 patients might experience thyrotoxicosis during their illness, however, most of them showed normal thyroid function after recovery. They also showed that the majority of cases were negative for anti-thyroid antibodies (97).

About 10 days later, the COVID-19 symptoms in a 49-year-old man with COVID-19 symptoms included mild fever, sore throat, shortness of breath in Guven's study, neck pain complications, inflamed tonsils, and fever. The performance of an ultrasound examination of the thyroid for the confirmation of subacute thyroiditis showed heterogeneous parenchyma, hypoechoic areas, and irregular infiltration. Laboratory tests of thyroid function showed normal fT3, fT4, and low TSH levels. Furthermore, the ESR

rate and CRP level were significantly high, supporting the onset of subacute thyroiditis (111).

A case with thyrotoxicosis was studied in another clinical case. This 69-year-old woman was diagnosed with COVID-19 following a positive PCR test and the appearance of clinical symptoms, including febrile cough and pneumonia. The patient was also involved with a longstanding non-toxic nodular goiter. However, this patient did not suffer from neck pain (probably due to the consumption of painkillers). The diagnosis of Subacute thyroiditis was made through other clinical symptoms and thyroid ultrasound which showed hypoechoic thyroid. Laboratory tests showed a decrease in the TSH level and an increase in the level of FT3 and FT4. The symptoms of subacute thyroiditis disappeared a few days after the initiation of corticosteroid treatment (112).

In another study conducted in Iran, six patients with clinical symptoms of subacute thyroiditis were referred. The sonographic features of the thyroid gland of all patients showed bilateral hypoechoic areas that supported the diagnosis of subacute thyroiditis. In addition, they had a high CRP and high ESR rate. The interesting point was that none of them were involved in the severe form of COVID-19. Two were asymptomatic, four had moderate and mild symptoms, and all were positive for anti-SARS-CoV2

IgM and IgG. These results suggest that subacute thyroiditis could also develop in outpatient patients with moderate COVID-19 and even asymptomatic patients. These cases received steroids and their condition resolved within one month from the onset of subacute thyroiditis (113).

Female patients (n=4) with such symptoms as neck pain, palpitations, fever, and asthenia were studied in another study. Thyroid ultrasonography showed enlarged thyroid glands with diffuse bilateral hypoechoic areas. Inflammatory indicators, such as ESR and CRP were elevated in these patients. Thyroid function test showed suppressed TSH and elevated T3 and T4, suggesting ongoing destructive thyroiditis. Symptoms of subacute thyroiditis resolved within days of starting the medications, and the laboratory indicators returned to normal within six weeks (114).

Other clinical cases have indicated the development of subacute thyroiditis following SRAS-CoV2 infections. According to the studies mentioned above, most of the clinical cases showed nearly similar results, such as increased T3 and T4 levels and suppressed or undetectable TSH levels along with the absence of antibodies against the TSH receptor (9,115-117). Table 1 presents a summary of the series of case studies and their main results.

**Table 1.** Case reports on subacute thyroiditis in SARS-CoV2 infected patients.

Author	Country	Cases	SARS-CoV2 detection method	Main findings
<b>Guven (110)</b>	Turkey	A 49-year-old man	Clinical symptoms, PCR, and chest CT	Sore throat Heterogeneous, Patchy infiltrations and Hypoechoic thyroid Fever (38.3oC), TSH<0.005µIU/ml, FT4=3.61ng/dl, FT3=4.24ng/dl, ESR=80mm/h, CRP=7.69mg/dl No TSH receptor, Antithyroglobulin, and Anti-thyroid peroxidase antibodies
<b>Ippolito (111)</b>	Italy	A 69-year-old woman with non-toxic nodular goiter	Clinical symptoms, PCR, and chest CT	No pain, Palpitations, Insomnia, and agitation Enlarged hypoechoic thyroid TSH=0.02 mU/l, FT4=29.7 pg/ml, FT3=5.6 pg/ml, Serum thyroglobulin = 187 µg/l No TSH receptor, antithyroglobulin, and anti-thyroid peroxidase antibodies
<b>Asfuroglu Kalkan (117)</b>	Turkey	A 41-year-old woman	Positive PCR with no clinical symptoms	Neck pain, Thyroid palpation, fever (38.5oC), ESR= 134 mm/h, CRP=134mg/L TSH<0.008 mIU/L, FT3=7.7 pmol/L, FT4= 25.7 pmol/L No TSH receptor, Antithyroglobulin, and Anti-thyroid peroxidase antibodies
<b>Campos-Barrera (114)</b>	Mexico	A 37-year-old woman	Respiratory symptoms and positive PCR	Neck pain and fatigue, Enlarged tender thyroid, ESR=72mm/h, CRP=60mg/l FT4=1.6ng/dl, Total T3= 211ng/dl No TSH receptor, antithyroglobulin, and anti-thyroid peroxidase antibodies
<b>Mattar (115)</b>	Singapore	A 34-year-old man	Mild clinical symptoms and positive PCR	Neck pain, Tachycardia, and Diffuse asymmetric goiter A hypoechoic Heterogenous area in thyroid CRP=122mg/l TSH <0.01 mU/L, FT3= 13.4 pmol/l, FT4= 41.8 pmol/L No TSH receptor, Antithyroglobulin, and Anti-thyroid peroxidase antibodies
<b>Brancatella (118)</b>	Italy	an 18-year-old woman	Mild respiratory symptoms and positive PCR	Neck pain, Tachycardia, Enlarged thyroid multiple hypoechoic areas in the thyroid ESR=90mm/h, CRP=6.9mg/l TSH<0.004mIU/L, FT3=8.7pmol/l, FT4=27.2pmol/l Positive antithyroglobulin, Negative anti-TSH receptor, and Anti-thyroid peroxidase antibodies
<b>Ruggeri (116)</b>	Italy	A 43-year-old woman	Mild symptoms and positive PCR	Neck pain, Fatigue, Tremors, and Palpitations, Enlarged hypoechoic thyroid, ESR=60mm/h, CRP=8.8mg/l TSH=0.006 mU/l, FT3=7.07ng/ml, FT4=2.69ng/ml, Tg=188pg/ml No TSH receptor, Antithyroglobulin, and Anti-thyroid peroxidase antibodies

## 9. Conclusion

The hypothesis that SARS-CoV2 may initiate subacute thyroiditis is supported by other autoimmune and inflammatory disorders, previous experience on the role of viruses in the pathogenesis of subacute thyroiditis, and studies on the inflammatory mechanism of SARS-CoV2 infection. Regarding the fact that the evidence in this regard comes from clinical cases, the question is that “how solid this hypothesis could be?” Retrospective studies and large-scale case-control studies could evaluate this possible correlation. However, the evidence so far suggests that subacute thyroiditis should be considered a later symptom of COVID-19.

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