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Case Report

A case series of subacute thyroiditis associated with COVID-19 infection

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Abstract

Subacute thyroiditis can be one of the clinical manifestations of COVID-19, as has been reported in several previous cases. ACEI receptors are found in several cells and tissues of the body, one of which is in thyroid follicular cells, thus making the thyroid gland a potential target for entry of the SARS-CoV-2 virus. This case series describes that subacute thyroiditis is one of the clinical manifestations of COVID-19. All patients underwent an anamnesis, physical examination, examination of serum thyroid hormone TSH and FT4, inflammatory markers (CRP), and thyroid ultrasound during hospitalization. In this case series, it was reported that 7 confirmed COVID-19 patients with positive RT-PCR results had clinical symptoms of hyperthyroidism; the most common symptom is palpitation with the onset of varying. The results of laboratory examinations in four patients showed a decrease in FT4 levels, while in 3 patients, the FT4 was within normal limits. In all patients, there was a decrease in TSH and an increase in inflammatory markers (CRP). In one patient, an ultrasound examination of the thyroid found thyroiditis. The patient gets antithyroid therapy, steroids and b-blocker drugs for rate control. Of patients with outcome, 6 (86%) recovered and 1 (14%) died. We report a case series of thyroiditis that can be a clinical manifestation of COVID-19 infection. Clinicians should be aware of the manifestations of thyroiditis in COVID-19 patients. Early diagnosis and early therapy will provide good outcomes for COVID-19 patients.

Keywords: COVID-19, SARS-CoV-2, subacute thyroiditis, viral thyroiditis.

Introduction

Subacute thyroiditis (De Quervain's thyroiditis (viral thyroiditis) is a self-limiting thyroid gland inflammation usually caused by a viral infection. Subacute thyroiditis manifests as clinical hyperthyroidism and subclinical hyperthyroidism. Clinical hyperthyroidism is defined by low or undetectable serum thyroid-stimulating hormone (TSH) levels, with elevated or total free thyroxine (T4) and triiodothyronine (T3) levels. In contrast, subclinical hyperthyroidism is defined as low or undetectable serum thyroid-stimulating hormone (TSH) levels, with normal free or total free thyroxine (T4) and triiodothyronine (T3) [1]. There are extrapulmonary clinical manifestations of COVID-19 infection, one of which is in the thyroid gland. Several mechanisms can cause subacute thyroiditis in COVID-19 patients through direct viral injury supported by ACE-2 receptors and TMPRSS2 mRNA expression in thyroid cells and inflammatory reactions due to viral infection [2]. This case series describes cases of subacute thyroiditis in patients with confirmed COVID-19 in 4 patients with clinical hyperthyroidism and 3 patients with subclinical hyperthyroidism.

Material and methods

All patients underwent an anamnesis, physical examination, examination of serum thyroid hormone TSH and FT4, inflammatory markers (CRP), and thyroid ultrasound during hospitalization.

Case description

1. Clinical hyperthyroid patient

Patient 1

A 70-year-old woman complained of fever and cough for 4 days before hospitalization. After 4 days of treatment at the hospital, the patient complained of palpitations and difficulty sleeping. Upon physical examination, there was a tremor in her upper limbs. RT-PCR testing of SARS-CoV-2 was positive. The patient had a previous history of hypertension and type 2 diabetes. The patient had no previous history of thyroid disorders and autoimmune diseases. The patient was diagnosed with confirmed severe COVID-19. On examination of FT4 and TSH, there was an increase in FT4 of 1.78 ng/dl (0.7–1.48) and a decrease in TSH of 0.116 IU/Ml. On other laboratory tests, blood glucose test: 213 mg/dl (<140), C-Reactive Protein: 103.6 mg/L (<0.5). The patient was diagnosed with clinical hyperthyroidism et causa Thyroiditis and received therapy with Dexamethasone 2×5 mg IV, PTU 3×100 mg and Propranolol 2×10 mg. During treatment, the patient improved clinically and outpatiently.

Patient 2

A 34-year-old man complained of weight loss and palpitations—complaints of palpitations along with other complaints like cough and anosmia. RT-PCR testing of SARS-CoV-2 was positive. The patient had no previous medical history. The patient had no previous history of thyroid disorders and autoimmune diseases. The patient was diagnosed with mild confirmed COVID-19 and suspected hyperthyroidism. On examination of FT4 and TSH, there was an increase in FT4 >5 ng/dl (0.7–1.48) and a decrease in TSH of 0.001 IU/Ml. The patient was diagnosed as hyperthyroid with suspected thyroiditis and received therapy with Methimazole 2×10 mg and propranolol 3×10 mg. During treatment, the patient improved clinically and outpatiently.

Patient 3

A 49-year-old man complained of fever 1 day before hospitalization. RT-PCR testing of SARS-CoV-2 was positive. The patient was diagnosed with moderate-grade confirmed COVID-19. He had underlying diseases such as hypertension, CAD, and dyslipidemia. After 3 months of recovering from COVID-19, He came with complaints of chest pain and tremors. The patient had no previous history of thyroid disorders and autoimmune diseases. On examination of FT4 and TSH, there was an increase in FT4 of 3.89 ng/dl (0.7–1.48) and a decrease in TSH of 0.009 IU/Ml. On laboratory examination, CRP 6.2 (H) was found. The patient received therapy with clopidogrel 1×75 mg and atorvastatin 1×20 mg and received treatment for 1 day in the hospital. During treatment, the patient improved clinically and outpatiently.

Patient 4

A 34-year-old woman complained of shortness of breath, palpitations, weakness, and weight loss for 3 weeks before hospitalization. Complaints of palpitations appear along with other complaints. RT-PCR testing of SARS-CoV-2 was positive. The patient was diagnosed with critical-grade COVID-19 pneumonia. The patient had no previous medical history. The patient had no previous history of thyroid disorders and autoimmune diseases. FT4 and TSH examination found that FT4 increased by 3.29 ng/dl (0.7–1.48), decreasing TSH by 0.025 IU/Ml. On other laboratory tests, CRP is 51.8 (H). The patient underwent an ultrasound examination of the thyroid with the impression that there was a picture of thyroiditis. The patient was diagnosed with hyperthyroidism et causa thyroiditis. The patient received therapy with dexamethasone 1×5 mg IV and methimazole 2×10 mg.

2. Cases of subclinical hyperthyroidism

Patient 1

A 35-year-old pregnant patient came with the main complaints of shortness of breath, cough, fever and chest palpitations 1 week before hospitalization. RT-PCR testing of SARS-CoV-2 was positive. The patient had no comorbid disease. There was no previous history of thyroid disorders or autoimmune disease. The patient was diagnosed with critical-grade COVID-19 at 23 weeks of pregnancy. On FT4 examination, normal results were 0.82 ng/dl (N) and decreased TSH Sensitive 0.236 IU/mL. Other laboratory results showed CRP 97.4 (H) ESR 42 mm (H). The patient was diagnosed with subclinical hyperthyroidism et causa thyroiditis. The patient received treatment in the ICU and was given medical therapy with steroids, methylprednisolone 2×40 mg IV, and B-blockers for rate control propranolol 4×10 mg. On the 10th day of treatment, the patient died.

Patient 2

A 78-year-old male came to our emergency unit with the main complaint of shortness of breath and chest

palpitations that had been getting worse since 2 days before hospitalization. RT-PCR testing of SARS-CoV-2 was positive. He has a history of hypertension. There was no previous history of thyroid disorders or autoimmune disease. ECG results from Arial Fibrillation RVR, Heart Rate 120–130×/minute. The patient was diagnosed with severe COVID-19 with comorbid hypertension. On FT4 examination, normal results were 1.39 ng/dl (N) and decreased TSH Sensitive 0.223 IU/Ml (L). Other laboratory results showed CRP 19.4 (H) and ESR level 120 mm (H). The patient was diagnosed with subclinical hyperthyroidism et causa thyroiditis. The patient received therapy with dexamethasone 2×3 mg and bisoprolol 2×2.5 mg.

Patient 3

A 55-year-old female patient came with the main complaints of fever, cough and shortness of breath. RT-PCR testing of SARS-CoV-2 was positive. On the 14th day of treatment, the patient complained of palpitations on her chest. The patient has a history of type 2 diabetes mellitus and hypertension. There was no previous history of thyroid disorders or autoimmune disease. Patients diagnosed with COVID-19 confirmed critical grade. On FT4 examination, normal results were 1.07 ng/dl (N) and decreased TSH Sensitive 0.171 IU/Ml (L). Another laboratory result was CRP 54.7 (H). The patient was diagnosed with subclinical hyperthyroidism et causa thyroiditis. The patient received therapy with dexamethasone 1×6 mg and propranolol 3×10 mg.

Results

In this case series, there were 7 patients who were confirmed positive for COVID-19 through the RT-PCR examination of the nasopharyngeal swab. In this case series, 7 patients ranged in age from the youngest, 34 years, to the oldest, 78 years, with 3 male patients (43%) and 4 female patients (57%). Every patient was diagnosed with the severity of COVID-19 disease, varying from mild to critical. The most common symptoms were palpitations; other clinical symptoms found were tremors, sleep disturbances, weight loss, weakness, and feelings of thirst and hunger—two patients presented with cardiovascular complications and tachyarrhythmia (atrial fibrillation). The comorbidities found in these patients were Hypertension, Type 2 Diabetes Mellitus, Dyslipidemia, and Coronary Artery Disease (CAD). In all patients, there was no history of thyroid disorders or previous autoimmune disorders. On laboratory examination, 4 patients found an increase in FT4 levels, while in 3 patients, FT4 was found within normal limits. All patients had decreased serum TSH levels and increased inflammatory markers (CRP) levels. In one patient, an ultrasound examination of the thyroid showed thyroiditis. Four patients were diagnosed with clinical hyperthyroidism et causa thyroiditis, and 3 patients were diagnosed with subclinical hyperthyroidism et causa thyroiditis. All clinical and medical supporting data are presented in Table 1 for clinical hyperthyroidism patients and Table 2 for subclinical patients. The positive result of RT-PCR testing of Sarcov-2 and a history of previous COVID-19 infection explains the relationship of subacute thyroiditis triggered by COVID-19 infection. The patient was treated with antithyroid drugs, Thiamizole (Methimazole) and Propylthiouracil, and steroids (dexamethasone and Methylprednisolone) as anti-inflammatory, and beta-blockers (propranolol) to control hyperthyroid symptoms. Six patients found clinical improvement with the outcome recovered and 1 patient died.

Discussion

Subacute thyroiditis (also known as De Quervain's thyroiditis, viral thyroiditis, subacute granulomatous thyroiditis, or giant cell thyroiditis) is a self-limiting thyroid gland inflammation usually caused by a viral infection. Several viruses (such as measles, mumps, rubella, coxsackie, adenovirus, chickenpox, cytomegalovirus, Epstein Barr virus, HIV, Hepatitis E, and influenza) are thought to trigger this disease, either directly or indirectly through the circulating viral genome or the presence of virus-specific antibodies [3, 4].

Subacute thyroiditis is primarily a clinical diagnosis supported by laboratory and imaging studies [3–5]. Clinical symptoms are correlated and combined with the results of laboratory examinations obtained an increase in clinical features correlated with a combination of tests erythrocyte sedimentation rate and CRP, decreased TSH levels, increased thyroid hormone levels (T4 and T3) and thyroglobulin concentrations; with low/absent titers of circulating thyroid peroxidase and thyroglobulin antibodies [3]. Anti-inflammatory agents are first-line therapy, with corticosteroids used in more severe cases [3].

In the THYROCOV study conducted in Italy, the frequency of thyrotoxicosis and hypothyroidism in non-ICU COVID-19 patients was 20.2% and 5.2%, respectively. Furthermore, based on the results of the meta-analysis,

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Table 1: Patient clinical, biochemical, and imaging features cases of clinical hyperthyroidism.

No.	COVID-19 severity	Symptoms of hyperthyroidism	Laboratory	Therapy	Outcome	Comorbid	History of hyperthyroidism	History of autoimmune disorders
Patient 1 Female, 70 years old	Severe	Palpitations, sleep disturbances, polydipsia, polyphagia	• Free T4: 1.78 ng/dL (H); • TSH Sensitive: 0.116 IU/Ml (L); • CRP: 103.6 mg/L (H) (<0.5).	• Propylthiouracil; • Propranolol; • Steroids: dexamethasone, methylprednisolone.	Recovery	• DM type 2; • Hypertension; • CHF; • CAD old inferior MCI.	No	No
Patient 2 Male, 34 years old	Mild	Weight loss, tachycardia	• Free T4: >5 ng/dL (H); • TSH Sensitive: 0.001 IU/Ml (L); • CRP: -	• Methimazolee; • Propranolol; • Steroids: dexamethasone.	Recovery	No	No	No
Patient 3 Male, 48 years old	Moderate	Weight loss, tremor, anxiety, sleep disturbance, fatigue	• Free T4: 3.89 ng/dL (H); • TSH Sensitive: 0.009 IU/Ml (L); • CRP: 6.2 (H).	-	Recovery	• Hypertension; • Dyslipidemia; • CAD.	No	No
Patient 4 Female, 55 years old	Critical	Palpitations, weight loss, sleep disturbances	• Free T4: 3.29 ng/dL (H); • TSH Sensitive: 0.025 IU/Ml (L); • CRP: 51.1 (H).	• Methimazole; • Steroids: dexamethasone, Methylprednisolone.	Recovery	No	No	No

Table 2: Patient clinical, biochemical, and imaging features cases of subclinical hyperthyroidism.

No.	COVID-19 severity	Symptoms of hyperthyroidism	Laboratory	Therapy	Outcome	Comorbid	History of hyperthyroidism	History of autoimmune disorders
Patient 1 Female, 35 years old	Critical	Palpitations	• FT4: 0.82 ng/dl (N); • TSH Sensitive: 0.236 IU/Ml (L); • CRP: 97.4(H); • ESR: 42 mm (H).	• Steroids: Methylprednisolone; • Propranolol.	Die	No	No	No
Patient 2 Male, 78 years old	Severe	Palpitations	• FT4: 1.39 ng/dl (N); • TSH Sensitive: 0.223 IU/Ml (L); • CRP: 19.4(H); • ESR: 120 mm (H).	• Steroids: Methylprednisolone, dexamethasone; • Bisoprolol.	Recovery	Hypertension	No	No
Patient 3 Female, 55 years old	Critical	Palpitations	• FT4: 1.07 ng/dl (N); • TSH Sensitive: 0.171 IU/Ml (L); • CRP: 54.7(H).	• Steroids: Methylprednisolone, dexamethasone; • Propranolol.	Recovery	Type 2 DM, Hypertension	No	No

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thyroid disease was found to be associated with an increased risk of severe COVID-19 infection [6]. Several reported cases of subacute thyroiditis following COVID-19 infection worldwide [7–11].

It is believed that SARS-CoV-2 can affect thyroid function in a variety of ways. The three reported effects of viral infection are (a) thyrotoxicosis (either subacute/painful thyroiditis or painless/atypical thyroiditis), (b) hypothyroidism [central or primary and (c) non-thyroidal illness syndrome (formerly) known as euthyroid sick syndrome]. This suggests that the effect of the virus on the thyroid gland is highly variable, and it is difficult to predict abnormalities on thyroid function tests (TFT) [12].

Some of the mechanisms of thyroid function disorders in COVID-19 infection are:

- *Inflammatory response, apoptosis, and local damage*. Infection with the SARS-CoV virus causes an inflammatory response in the host [13] and induces apoptosis through the expression of several viral proteins [14, 15]. An autopsy study of 5 SARS patients conducted in 2007 found follicular epithelial damage and cell apoptosis in the absence of neutrophilic cell infiltration or lymphoid cells [16]. Apoptotic cells have been found in the liver and thyroid tissue of SARS-CoV patients [17]. In COVID-19 patients, inflammatory infiltrates have been found in various tissues, including the thyroid [18], thus supporting the potential role of inflammation.
- *Virus replication*. SARS-CoV and SARS-CoV-2 viral genomes have been found in the serum of patients [19]. The SARS-CoV virus was not isolated in the thyroid gland but was infiltrated through inflammatory cells [20, 21]. Other viral infections associated with thyroiditis have been associated with the presence of virus-like particles in thyroid tissue [4].
- *SARSCOV2 receptor ACE2 mRNA in thyroid cells*. Angiotensin-converting enzyme 2 (ACE2) is expressed in organs other than the lungs, including the thyroid [22, 23]. A study by Rotandi *et al*. showed that the mRNA encoding for the ACE-2 receptor is expressed in thyroid follicular cells, thereby targeting the thyroid gland potential for entry of the SARS-CoV-2 virus. In this study, the expression levels of ACE-2 mRNA were evaluated in 15 different thyroid tissue specimens and two primary thyroid cell cultures. ACE-2 mRNA was detected in all these thyroid tissue samples [24]. Sars-Cov 2 virus will enter the host through the ACE-2 receptor, which will then replicate and transmit the virus [25–27].
- *Central mechanism potential*. In patients infected with SARS-CoV-2, changes in thyroid hormone levels and thyroid gland dysfunction occur [28, 29]. A previous study reported decreased thyroid hormone levels and decreased TSH levels [28]. The decrease in hormone levels could be explained by pathological findings of follicular damage. However, low TSH levels could be secondary to hypothalamic-pituitary dysfunction – this is corroborated by the findings of central hypothyroidism and hypocortisolism in SARS patients [29, 30]
- *Cytokine storm syndrome*. Although it is well documented that these storms cause non-thyroidal illness syndrome in COVID-19 patients, there is currently little evidence to suggest a direct cytotoxic effect of cytokines on the thyroid, at least in humans [31–33].

Viral-mediated post-infection inflammatory reactions, involving both the adaptive and innate immune systems, have also been described in the literature as the cause of thyroid problems [1, 16]. This mechanism may be responsible for the post-infectious SAT observed in most patients.

Cases of subacute thyroiditis following COVID-19 infection were previously reported in cases of women varying in age from the youngest age of 18 years [4] to the oldest age of 69 years without medical comorbidities. In a systematic review study by Rehman *et al*., [21] cases of thyroiditis in COVID-19 were found; the average age of the patients was 40.0±11.3 years, with 71.4% female patients [1]. In this case series, 3 patients were male (43%), and 4 patients were female (57%), with the youngest age range being 34 years to the oldest 78 years. The comorbidities found in these patients were Type 2 Diabetes Mellitus, Hypertension, Dyslipidemia, and Coronary Artery Disease (CAD). It was found in previous studies that thyroid dysfunction is more common in people with diabetes par, particularly in type 1 diabetes. The relationship between thyroid disorders and diabetes mellitus is characterized by complex interdependent interactions. Insulin resistance status can increase thyroid gland nodularity, and coexisting diabetes can increase the risk of visual loss in patients with Graves' Disease [34].

The clinical symptoms in these four cases were most commonly palpitations; other clinical symptoms were fever, tremors, sleep disturbances, weight loss, and fatigue—two patients presented with cardiovascular

complications and tachyarrhythmia (atrial fibrillation). In the previous case report, clinical symptoms were neck pain, odynophagia, fever, palpitations, insomnia, tremors, dyspnea, fatigue and agitation [7–11]. In this case series, 5 patients had symptoms of hyperthyroidism along with symptoms of COVID-19 infection, while one case of hyperthyroidism symptoms appeared on the 14th day of treatment and in another case, symptoms of hyperthyroidism appeared 3 months after being infected with COVID-19. In the case report of Dr. Brancatella [7] reported symptoms occurring after 2 weeks of SARS-CoV-2 infection; 1 patient [10] had symptoms 6 weeks after infection, while the other 2 patients had a concurrent diagnosis of COVID-19 and thyroiditis [8, 9].

On FT4 and TSH examination in 4 patients, there were increased FT4 levels and decreased serum TSH levels and increased levels of inflammatory markers (CRP), while in 3 other patients, FT4 levels were within normal limits, but decreased serum TSH levels and increased levels of inflammatory markers (CRP). In one patient, an ultrasound examination of the thyroid showed thyroiditis. In the previous case report, the results of laboratory examinations of all patients showed the impression of thyrotoxicosis, increased inflammatory markers ESR and CRP, and ultrasound showed hypoechoic thyroid suggestive of thyroiditis [7–11].

In several previous case reports, all patients responded well to anti-inflammatory therapy and corticosteroids [7–11]. A systematic review study by Rehman *et al.* showed that all thyroiditis patients with COVID-19 were treated with steroids and anti-inflammatory drugs, and all patients reported symptom resolution, but 5 patients (23.8%) reported hypothyroidism complaints at follow-up [1]. The patient in this case series was treated with the antithyroid thiazole and Propylthiouracil and steroids (dexamethasone) as an anti-inflammatory. In this case series, 3 patients with clinical hyperthyroidism were treated with antithyroid drugs such as methimazole and propylthiouracil because these patients had significant hyperthyroidism symptoms. In 6 patients, there was clinical improvement and recovery, while 1 patient clinically worsened and died during treatment in the ICU.

There is no definitive treatment for subacute thyroiditis. Effective treatment will improve symptoms and allow the disease to progress spontaneously without symptoms. Some literature describes the treatment of subacute thyroiditis using nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids. Nonsteroidal anti-inflammatory drugs have been used in patients with mild or moderate forms of the disorder. In more severe conditions, oral glucocorticoids in various pharmacological doses have been reported to provide rapid relief of pain and fever within 24–48 hours. Prednisolone is the most commonly used glucocorticoid in treating subacute thyroiditis [35].

We report a case series of thyroiditis that can be a clinical manifestation of COVID-19 infection. Direct viral injury through ACEI-2 receptors on thyroid follicular cells and inflammatory reactions are some of the mechanisms for subacute thyroiditis during COVID-19 or post-COVID-19 infection. In this case report, there are patients with clinical manifestations of hyperthyroidism and subclinical hyperthyroidism. In this case report, it was found that 6 patients (86%) recovered and 1 patient (14%) died. The treatment of subacute thyroiditis in COVID-19 patients and non-COVID patients is the same, using antithyroid hormones, steroids, and B-blockers as rhythm control. Clinicians should be aware of the manifestations of thyroiditis in COVID-19 patients. Early diagnosis and early therapy will provide good outcomes for COVID-19 patients.

In this case series, there are several limitations. Firstly, cases are only taken at a single center so that the number of patients obtained is not large; secondly – laboratory and imaging examinations are limited due to health insurance protocols and limited facilities, and in this case series, we did not followed-up the patients, so we suggest that in the future, case series can follow-up thyroiditis patients with COVID-19.

Conclusions

We report a case series of thyroiditis that can be a clinical manifestation of COVID-19 infection. Direct viral injury through ACEI-2 receptors on thyroid follicular cells and inflammatory reactions are some of the mechanisms for the occurrence of subacute thyroiditis during COVID-19 or post-COVID-19 infection. In this case report, there are patients with clinical manifestations of hyperthyroidism and subclinical hyperthyroidism. In this case report, it was found that 6 patients (86%) recovered and 1 patient (14%) died. The treatment of subacute thyroiditis in COVID-19 patients and non-COVID patients is the same, using antithyroid hormones, steroids, and B-blockers as rhythm control. Clinicians should be aware of the manifestations of thyroiditis in COVID-19 patients. Early diagnosis and early therapy will provide good outcomes for COVID-19 patients.

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Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The research met our institutional definition of a case report; thus, an institutional research board review was unnecessary.

Consent to participate

Written informed consent was obtained from all participants in this study.

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