

Subacute Thyroiditis Following COVID19 Vaccine: Report of Four Cases

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Abstract

An increase in the incidence of subacute thyroiditis (SAT) following the COVID-19 vaccine. The aim of this report is to shed the light on different presentations of SAT postCOVID-19 vaccine while reviewing the link between the vaccine and subsequent thyroid inflammation. We present the case of a middle-aged man who presented symptoms of SAT 1-week postvaccine. He achieved euthyroidism 6 weeks later. We also present the case of a middle-aged woman with less severe symptoms of SAT 4 weeks after the vaccine. She is in the hypothyroid phase 11 weeks later. A 37-year-old male developed severe symptoms 2 weeks after the first dose and is still hyperthyroid 5 weeks later. A 36-year-old woman presented with silent SAT 3 weeks after the first dose. Cases of SAT following SARS-Cov-2 are now reported increasingly. COVID-19 can cause thyroiditis via direct cell, or alternatively through immune destruction of the thyroid in genetically susceptible individuals. Similarly, the vaccine can promote inflammation through the same mechanisms. Indeed, there is a postulated cross-reactivity between the spike protein and thyroid antigens. More-so, there is the studied vaccine adjuvant effect on the endocrine system, namely the thyroid in this case. Cases of SAT postCOVID-19 vaccines are increasingly reported. Theories are similar to COVID19-induced thyroiditis but also other mechanisms are uniquely mediated by vaccines. A low threshold should be set to diagnose SAT in patients with one or more hyperthyroid symptoms presenting 1–8 weeks postCOVID-19 vaccine.

Keywords: COVID-19, COVID-19 vaccination, subacute thyroiditis, thyroid, thyroiditis

INTRODUCTION

Subacute thyroiditis (SAT) is a rare form of generally painful thyroid disease. Its estimated prevalence is equal to 12/100,000/year, more common in middle-aged women.^[1] Its most common clinical manifestations include, in the first phase, anterior neck pain that radiates to the jaw and ears, fever, fatigue, and malaise in addition to clinical manifestations of hyperthyroidism (such as weight loss, tremor, and palpitations). The second phase is characterized by subclinical hypothyroidism, with few to no symptoms. In the minority of patients, hypothyroidism persists and requires prolonged therapy. Many recent reports provide a direct link between COVID-19 and the development of thyroiditis.^[1–4] In addition, thyroiditis is increasingly documented following vaccination against COVID-19. To provide more insight on the topic, we hereby present four cases of SAT occurring up to 8 weeks following the COVID19 vaccine. Cases vary in severity, presentation, and course. A literature review detailing the pathogenesis of SAT and the effect of the vaccine on its development is presented as well.

CASE REPORTS

The salient clinical features, management and outcomes of the case series are summarized in Table 1. Details of all the cases are described fully below.

Case 1

A 45-year-old man presented for 1 week of neck pain; pain was localized to the base of the neck, radiating to the right ear and worsening with swallowing. It was accompanied by fever and heat intolerance. He had received Pfizer vaccine 1 week before the onset of the symptoms. Pain has resolved with nonsteroidal anti-inflammatory (NSAIDs) for 4 days.

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How to cite this article: El Ghandour S, Al Ghazal N. Subacute thyroiditis following COVID19 vaccine: Report of four cases. *J Diabetes Endocr Pract* 2021;4:206-9.

Received: 14-10-21

Revised: 27-10-21

Accepted: 27-10-21

Web Published: 30-12-21

Access this article online

Quick Response Code:



Website:
www.jdeponline.com

DOI:
10.4103/jdep.jdep_46_21

His physical exam was positive for enlarged mildly tender thyroid and fine tremor in both hands. His ultrasound showed a picture of active thyroiditis mainly at the right thyroid lobe and to less extent at the left lobe with reactive lymphadenopathy [Figure 1]. Laboratory investigations revealed thyroid-stimulating hormone (TSH) <0.01 , Free T4 level 28 (normal 9.00–19.04 pmol/L), free T3 8.92 pmol/L (normal 2.60–5.70 pmol/L), C-reactive protein (CRP) 97.5 mg/L (normal <5.00 mg/L), mild neutrophilia white blood cell count $10.5 \text{ K}/\mu\text{L}$ with 67% neutrophils. Six weeks later, he was back to clinical and biochemical euthyroidism.

Case 2

A 43-year-old woman presented with progressive palpitations, heat intolerance, and fatigue. On questioning, she noted neck discomfort, specifically upon swallowing. She had received 2 doses of Pfizer vaccine 7 weeks before presentation and around 4 weeks before symptoms onset. Her heart rate was 110 beats/min at rest and her thyroid was homogeneous but firm on examination. Her laboratories confirmed hyperthyroidism and her ultrasound showed diffusely heterogeneous thyroid with coarse echotexture and prominent hyperemia. CRP was mildly elevated and TSH receptor antibody (TRAB) was negative. She was given beta-blockers. 4 weeks later, she was in the hypothyroid phase TSH 6.2, Free T3 (normal 2.60–5.70 pmol/L) 3.4, free T4 9.4 28 (normal 9.00–19.04 pmol/L) with positive anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies.

Case 3

A 36-year-old male presented with neck pain that started 2 weeks after the first dose of Pfizer. He was seen in the clinic 4 weeks after the second dose with persistent neck pain, palpitations, and flare of his anxiety. He was already on NSAIDs and beta blockers. His exam was significant for a firm thyroid. His laboratories confirmed hyperthyroidism TSH 0.005, Free T3 of 13.4 pmol/L (normal 2.60–5.70 pmol/L), Free t4 of 46 (normal 9.00–19.04 pmol/L). His liver function tests were

elevated. Erythrocyte sedimentation rate (ESR) and CRP were both elevated, at 40 mm/h (normal 2–30) and 39 mg/L (normal 0–5), respectively. His ultrasound was suggestive of active thyroiditis. TRAB, anti-TPO, and anti-TG were negative. He was started on steroids and beta-blockers were continued.

Case 4

A 37-year-old woman presented with menorrhagia and a suppressed TSH = 0.019 uIU/mL (normal range 0.15–4.94) 3 weeks after the first dose of Pfizer vaccine. She reports no neck discomfort but unusual fatigue and new-onset tremor with movement. Her resting heart rate was 118 beats/min. Labs confirmed subclinical hyperthyroidism with normal free T4 and Free T3 levels, 13.60 pmol/L (normal 9.00–19.04 pmol/L) and 4.29 pmol/L (normal 2.60–5.70 pmol/L), respectively, and high CRP 13 mg/L (normal range 0.0–5.0). TRAB was negative. She was treated with beta-blockers. Her ultrasound showed increased vascularity on color Doppler [Figure 2].

DISCUSSION

The cases presented in this report range from nonpainful “silent” thyroiditis to symptomatic prolonged hyperthyroid phase requiring steroids. Though rare, nonpainful thyroiditis has been reported postCOVID19. Endpoints were also different ranging from rapid recovery to prolonged hyperthyroidism to hypothyroidism.

SAT is a spontaneously remitting inflammatory disorder of the thyroid. Patients characteristically present with severe pain, swelling, and tenderness in the thyroid region, accompanied by malaise, fatigue, myalgia, and arthralgia. There is usually an initial thyrotoxic phase with raised inflammatory markers, followed by a hypothyroid phase and then a recovery phase. Symptoms are generally self-limiting. However, the neck pain can be severe and persistent, requiring a short course of steroid therapy.^[1,5]

ESR and CRP are usually elevated. Serum thyroglobulin concentrations are elevated due to its release from the thyroid gland. Anemia, leukocytosis, and elevated liver function tests are also frequently recorded. Radioiodine or

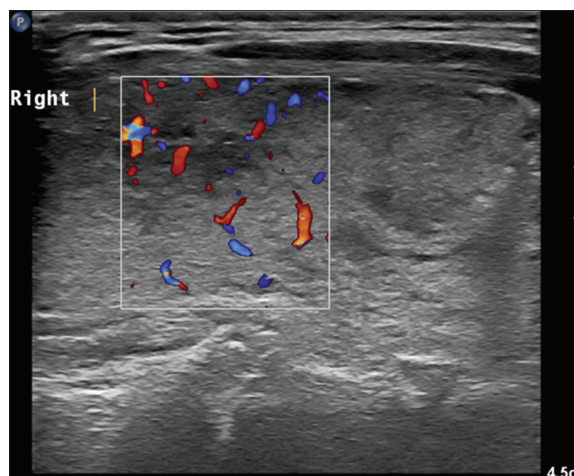


Figure 1: The thyroid ultrasound of case 1 showing a picture of active thyroiditis mainly at the right thyroid lobe and to less extent at the left lobe with reactive lymphadenopathy

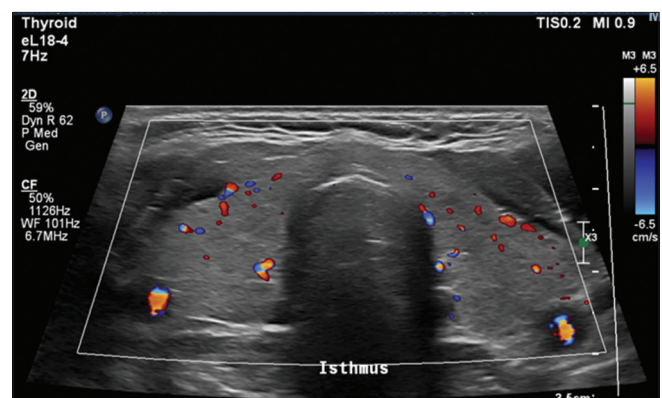


Figure 2: Thyroid ultrasound of Case 4 showing increased vascularity on color Doppler

Table 1: Salient features and outcome of the four cases

Age (years)	Sex	Features	Outcome
45	Male	Neck pain Clinical and biochemical hyperthyroidism Elevated inflammatory markers Symptoms started 1 week postvaccination	Biochemical euthyroidism and resolution of symptoms at 6 weeks. Resolution of neck pain with NSAIDs
43	Female	Symptoms of hyperthyroidism Biochemical hyperthyroidism followed by hypothyroidism Symptoms occurred 3 weeks postvaccination	Treated for hypothyroidism
36	Male	Neck pain Clinical and biochemical hyperthyroidism Elevated inflammatory markers Symptoms started 4 weeks postvaccination	Neck pain requiring steroids, resolved after 75 days Biochemically euthyroid after 75 days
37	Female	Clinical signs of hyperthyroidism Subclinical hyperthyroidism on laboratory testing Symptoms occurred 1 week postvaccination	Symptomatic treatment to control symptoms

NSAIDs: Nonsteroidal anti-inflammatory diseases

technetium imaging studies will show low or absent uptake. On ultrasonography, the thyroid appears to be normal or enlarged with the increased flow on colored Doppler sonography.

SAT usually occurs following a trigger, most commonly a recent viral infection 2–6 weeks before thyroiditis. The most reported viruses thought to be inducing SAT are Coxsackie viruses, Echoviruses, adenoviruses, influenza viruses, mumps and rubella viruses, parvovirus B19 viruses, orthomyxoviruses, HIV, EpsteinBarr viruses, hepatitis E, and measles viruses. More recently SARS-Cov-2 pandemic has added COVID-19 as one of the possible agents that can trigger SAT.^[6]

COVID-19 is a novel coronavirus identified in 2019 in the city of Wuhan, China. It has resulted in rapid spread leading to a world pandemic. The clinical spectrum of COVID-19 infection ranges from asymptomatic infection to critical and fatal illness.

In a systemic review of the literature included 1237 patients admitted with COVID infection to the prevalence of thyroid dysfunction was estimated to reach 64% with a direct correlation to the a severity of the infection.^[6]

Multiple mechanisms have been postulated trying to explain the direct effect of the virus on the thyroid gland. Three of them will be highlighted here. First, COVID-19 has been shown to cause direct damage to thyroid cells; this process is mediated by angiotensin-converting enzyme 2 (ACE2), a type I transmembrane metallo-carboxypeptidase involved in the Renin-Angiotensin pathway, which enables the virus to enter thyroid follicular cells.^[7] ACE-2 mRNA was detected in surgical thyroid tissue samples in 15 patients undergoing thyroidectomy for benign thyroid nodules, therefore supporting the theory of expression of ACE-2 in thyroid cells.^[8] The second hypothesis is molecular mimicry, i.e., molecular peptides presented by the virus are similar to thyroid peptides causing cross-reactive immune response generating autoreactive T-cells that promote an autoimmune response against the thyroid.^[8] Although COVID-19 has been most commonly linked to SAT, some reports have documented its implication in Grave's disease and Hashimoto

thyroiditis. The third hypothesis is the destruction of thyroid cells by the immune system. SAT is associated with human leukocyte antigen (HLA)-B35, which may be virally induced in genetically predisposed individuals.^[8,9] Other alleles were also identified in subsequent studies confirming the genetic predisposition for SAT in almost all patients.^[5] Hence, the expression of viral antigens by thyroid host cells will lead in genetically-susceptible individuals who are HLA-B35 positive, to autoimmune destruction of thyroid cells. This hypothesis was backed-up by documenting the presence of HLA-B35 in 70% of patients with SAT.^[5]

Since the spread of COVID19 infection, various vaccines have become available in different countries. In the United States, the COVID19 mRNA vaccines BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) and mRNA 1273 (Moderna COVID-19 vaccine) and the COVID-19 adenovirus vector vaccine Ad26.COV2.S (Janssen COVID-19 vaccine) have received emergency use authorization for use in individuals 18 years and older. Other types of vaccines have emerged as well. As an example, inactivated vaccines are produced by growing SARS-CoV-2 in cell culture then chemically inactivating the virus. The inactivated virus is often combined with alum or another adjuvant to stimulate an immune response.

Several case reports have emerged recently documenting thyroid dysfunction, mostly thyroiditis in patient who received COVID19 vaccination. Oyibo reported the case of 55-year-old who presented with neck pain, swelling, and thyrotoxicosis, 3 weeks after receiving her first dose of the COVID-19 vaccine (ChAdOx1 nCoV-19 vaccine, AstraZeneca)^[2] Iremli *et al.*, reported 3 cases of SAT after inactivated SARS-CoV-2 vaccine (CoronaVac®). Franquemont *et al.* reported the case of a 42-year-old woman with no past medical history developing thyroiditis following the receipt of Pfizer/BioNTech mRNA vaccine for COVID-19.^[3]

Hypotheses explaining the causative mechanism of COVID19 vaccination and thyroiditis stem back to the same principles explaining the direct effect of COVID19 infection on the

thyroid itself. Cross recognition between COVID19 spike protein targeted with the mRNA vaccine and healthy thyroid cell antigens exists, causing autoreactive T-cells that promote an autoimmune response against the thyroid. An additional theory to the ones previously explaining COVID19-induced SAT is the effect of adjuvants on the endocrine system in general and the thyroid gland in particular. Adjuvants are additives made to increase the immune response to vaccines; they were shown to cause autoimmune and inflammatory reactions by stimulating immunogenic cross-reactivity in genetically susceptible individuals.^[3] Autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome) has been described in the literature many years ago. ASIA syndrome has been previously reported to occur following vaccines against human papillomavirus, hepatitis B, and influenza. This immune reactivation might target the endocrine system causing type 1 diabetes, premature ovarian failure, autoimmune thyroiditis, adrenal insufficiency, and SAT as well.^[3,10-12]

CONCLUSIONS

Cases of SAT post COVID19 vaccines are increasingly reported. Theories are similar to COVID19 induced thyroiditis but also other mechanisms are uniquely mediated by vaccines. The patient presentation can vary from severe painful goiter to minimal or un-noticeable discomfort. Thyroiditis might be prolonged with weeks of hyperthyroidism, or quickly resolves or ends in transient or permanent hypothyroidism. One should have a low threshold to diagnose SAT in patients with one or more hyperthyroid symptoms presenting 1–8 weeks postCOVID19 vaccine.

Declaration of patients' consent

The authors certify that they have obtained the appropriate patients' consent. The patients have given consent for images and other clinical information to be reported in the journal. The patients understand that no names and initials will be published, and all due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authors' contribution

Both authors have contributed to the published work to fulfill the ICMLE authorship criteria. They both approved the final version of the article.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles:

No prior ethical approval is required for case reports and small case series provided the patients provide consent as stated above.

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