Endocrinology, Diabetes & Metabolism CASE REPORTS

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ID:21-0193;September2022
DOI: 10.1530/EDM-21-0193

Subacute thyroiditis post viral vector vaccine for COVID-19

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Summary

Subacute thyroiditis is an inflammatory disorder of the thyroid gland that has previously been described following viral illnesses and occasionally post vaccination such as influenza vaccine. 2021 was a revolutionary year for the development of SARS-CoV-2 vaccinations with multiple different vaccines now available. There are increasing numbers of case reports of thyroiditis following these vaccinations. We report a case of a 50-year-old female who developed subacute thyroiditis 6 days post ChAdOx1 nCoV-19 vaccine (AZD1222 produced by AstraZeneca Vaxzevria). The initial thyrotoxic phase was followed by overt hypothyroidism. This resolved spontaneously within 5 months without levothyroxine replacement. We hope that our case will add to the growing literature of cases of thyroiditis occurring after multiple different types of SARS-CoV-2 vaccination and create awareness of this rare but treatable adverse effect. We also review the literature on the proposed mechanisms behind this adverse effect.

Learning points

- Subacute thyroiditis is an inflammatory disorder of the thyroid gland that can occur after a viral illness or vaccination against certain infections.
- Subacute thyroiditis is a rare adverse effect that has been reported to occur after different types of SARS-CoV-2 vaccinations.
- Subacute thyroiditis post vaccination is relatively straightforward to manage, with some patients requiring non-steroidal anti-inflammatory drugs and beta-blockers, while more severe cases may require corticosteroid therapy. This adverse effect should not dissuade vaccination use at a population level.
- There are many postulated mechanisms for the development of subacute thyroiditis following vaccination including the presence of the ACE-2 receptor for SARS-CoV-2 on the thyroid gland, an inflammatory/immune response as is seen in COVID-19 infection itself and molecular mimicry between SARS-CoV-2 spike protein and healthy thyroid antigen.

Background

Since early 2020, the entire globe has been thrown into turmoil with the arrival of SARS-CoV-2. Our health systems have faced considerable challenges, and unprecedented demands have been placed on our scientists and medical professionals to create a vaccination to end this pandemic. Thankfully this demand was successfully met and multiple different vaccines are now available. One of these vaccines is the ChAdOx1 nCoV-19 vaccine which was developed by the University of Oxford and AstraZeneca. It is an adenoviral vector vaccine that works by delivering the genetic code of the SARS-CoV-2 spike protein to human cells to provoke an immune response (1). It was authorised for use in the European Union on 29/1/2021 by the European Medicines Agency (2).

Subacute thyroiditis (de Quervain's thyroiditis) is an inflammatory disorder of the thyroid gland characterised

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by a painful thyroid gland, elevated inflammatory markers and abnormal thyroid function tests – often with a low thyroid-stimulating hormone (TSH) +/− elevated free thyroxine (FT4) (3, 4). Approximately 50% of the patients will have an initial thyrotoxic phase due to the unregulated release of preformed thyroid hormone from damaged follicular cells (4). Patients may have a prodrome of malaise, fever, pharyngitis symptoms and fatigue (4). Radioactive iodine uptake is low and thyroid ultrasound, if done, shows diffuse heterogeneity, focal hypoechoic areas and decreased or normal colour flow doppler, rather than enhanced flow characteristic of Graves' disease (4). The thyrotoxic phase may last 3–6 weeks, and then 30% of the patients will enter a hypothyroid phase that can last up to 6 months, and 5–15% may have persistent hypothyroidism (4).

Sub-acute thyroiditis is most often preceded by a viral infection. Multiple etiologic agents have been implicated including mumps, Epstein–Barr virus, influenza and adenovirus (3). There have also been case reports of thyroiditis following vaccinations. For example, Girgis *et al*. reported a case of a 36-year-old female who developed thyroiditis 4 weeks following the H1NI vaccine (5).

Treatment is usually with beta-blockers and non-steroidal anti-inflammatory drugs (NSAIDs). Corticosteroids can be used if there is failure of response to NSAIDs or if moderate-to-severe pain and thyrotoxic symptoms (4). Levothyroxine may be employed during the hypothyroid phase but should be withdrawn after 3–6 months with repeat thyroid function testing.

We report a case of subacute thyroiditis post ChAdOx1 nCoV-19 vaccine and review some of the literature on this adverse effect. We aim to increase awareness of this rare but treatable adverse effect reported after COVID- 19 vaccinations.

Case presentation

A 50-year-old female presented with malaise and neck pain 6 days after the first dose of ChAdOx1 nCoV-19 vaccine (AZD1222 produced by AstraZeneca Vaxzevria®). She had also noted swelling in the anterior aspect of her neck. She reported feeling well prior to vaccination.

She had a past medical history of uterine fibroids and seborrheic dermatitis. She was on no regular medications and had no known drug allergies.

She had a family history of thyroid disease with her mother having hyperthyroidism of uncertain aetiology.

On examination, she had anterior neck tenderness but no goitre or clinical features of thyrotoxicosis.

Investigations

Initial laboratory investigations showed a low TSH with an elevated free triiodothyronine (FT3). C-reactive protein was elevated at 73 mg/L. Full blood count and renal profile were normal. Repeat blood test 3 months later showed overt hypothyroidism (Table 1). Anti-thyroid peroxidase (TPO) antibodies were positive 6.9 IU/mL (range <5.61 IU/mL Abbott). TSH receptor antibody was negative.

Treatment

She was referred to our endocrinology department and the working diagnosis was felt to be subacute thyroiditis, likely related to her recent COVID-19 vaccination. She was initially managed conservatively with over-the-counter NSAIDs as required and then offered treatment with levothyroxine replacement when she became hypothyroid; however, she declined same.

Outcome and follow-up

Her thyroid function tests were followed closely, and thankfully she is now euthyroid on two subsequent thyroid function test measurements and is asymptomatic (Table 2).

Her case was reported to the health products regulatory authority and to Astra Zeneca.

Discussion

Vaccines have revolutionised the international battle against the COVID-19 pandemic. As with any treatment, adverse effects have been reported but broadly speaking the benefits have outweighed the risks at a population level. In November 2021, it was estimated that COVID-19 vaccination had already saved almost half a million lives in those aged over 60 in the World Health Organization (WHO) European region (6). With almost 12 billion vaccine doses now administered worldwide, we are learning more about these vaccines and what adverse effects to be aware of (7).

Table 1 Pattern of thyroid function tests prior to presentation and at presentation.

Date	**TSH** (ref. range: 0.35–4.94 mIU/L)	**Free T4** (ref. range: 8–22 pmol/L)	**Free T3** (ref. range: 2.43– 6.01 pmol/L)
03/2018	0.44	14	
03/2021	0.03	18	6.51
06/2021	47.37	9	

TSH, thyroid-stimulating hormone; Ref. range, reference range; T4, thyroxine; T3, triiodothyronine.

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Table 2 Follow-up thyroid function tests.

Date	**TSH** (ref. range: 0.35–4.94 mIU/L)	**Free T4** (ref. range: 8–22 pmol/L)
08/2021	3.29	12
11/2021	2.40	12

TSH, thyroid-stimulating hormone; T4, thyroxine.

There are case reports of subacute thyroiditis occurring following many of the COVID-19 vaccinations – including adenoviral vector vaccination, mRNA vaccination and inactivated SARS-CoV-2 vaccination (8, 9). Ippolito *et al*. published a systematic review of the case studies to date (10). Most of these cases were following mRNA vaccines (66%); however, 18% were associated with viral vector vaccines as in our case and 6% were associated with inactivated virus vaccines. The median age of patients was 39.5 years and the median time to onset was 10 days. Our case involved a 50-year-old female and 74% of these cases in the systematic review involved a female suggesting that this adverse effect is more prevalent in females. Women have previously been shown to be three to five times more likely to be affected than men by thyroiditis (4). Our patient had positive anti-TPO antibodies compared with only 8% of patients in the systematic review. Our patient required minimal medical intervention; however, over half of the patients (56%) required corticosteroid therapy, suggesting a more severe episode of thyroiditis. Treatment for subacute thyroiditis can vary, and it is important to take patient preference into account. The patient in our case was keen to avoid any medical therapy if possible. Ippolito *et al*. have suggested that a prior history of thyroid disease may predispose to subacute thyroiditis post mRNA vaccines, but larger studies would be needed to confirm this.

The effect of COVID-19 infection itself on the thyroid gland has also been a topic of interest in the literature. Ruggeri *et al*. discuss the immune and inflammatory thyroid disorders related to SARS-CoV-2 (11). The authors discuss how thyroid dysfunction may occur as both a direct and indirect effect of SARS-CoV-2 on the gland. The direct effect may be explained by the ACE-2 receptor which has become a commonly discussed topic in COVID-19 conversations. It is the mechanism of entry of the virus into the host cells and indeed it is highly expressed in thyroid follicular cells (11, 12). Alternatively, thyroid inflammation may be related to the 'cytokine storm' seen in severe COVID-19 infection. COVID-19 infection can lead to systemic inflammatory and immune response involving T helper lymphocytes (Th1/Th17/Th2) lymphocytes and proinflammatory cytokines that resemble immune activation seen in immune-mediated thyroid diseases (11). COVID-19-related thyroid disorders include destructive thyroiditis and onset or relapse of autoimmune thyroid disorders as well as alterations in thyroid function due to non-thyroidal illness (11). Elevated levels of interleukin-6 (IL-6) in COVID-19 have been shown to be associated with destructive thyroiditis, which suggests that thyroid gland inflammation may be triggered by the cytokine storm associated with COVID-19 (13). IL-6 levels have also been shown to correlate with disease severity and indeed COVID-19 patients with thyrotoxicosis have been shown to have a poorer prognosis and extended hospital stay (13). Ruggeri *et al*. found significant variability in the prevalence of subacute thyroiditis in COVID-19 which was reported as high as 20% in the THYRCOV study, whereas other studies showed that thyroid function test abnormalities related to non-thyroidal illness were more prevalent (11, 13, 14). The variability may be explained by the heterogeneity of the studies including patient setting and limitations such as interference of medication with thyroid function test measurements (11).

It can be postulated that the mechanism of development of thyroiditis post SARS-CoV-2 vaccination may be related to the above direct and indirect effects. Vojdani *et al*. have also demonstrated possible molecular mimicry with structural similarity noted between SARS-CoV-2 spike protein and thyroid peroxidase (11, 15). Many of the COVID-19 vaccinations employ this spike protein to create an immune response. There may be cross recognition of virus and healthy thyroid antigen cells, and furthermore, cross-reaction between SARS-CoV-2 antibodies and thyroid peroxidase antibodies (15). A genetic predisposition has also been proposed – HLA B35 haplotype has previously been associated with development of thyroiditis (16). The autoimmune/inflammatory syndrome induced by adjuvants is a recognised condition thought to occur due to adjuvants used in vaccines to enhance the immune response and has also been reported to be a possible contributor to subacute thyroiditis post vaccination (9).

A recent study by Oğuz *et al*. also discussed the pertinent topic of repeat vaccination in patients who develop this side effect. Although this was a small cohort, it showed that seven out of nine patients had no exacerbation/recurrence of subacute thyroiditis after repeat vaccination (17). Unfortunately, the patient in our case was reluctant to consider repeat vaccination due to the adverse effect she experienced after her first vaccination.

It is important to create awareness of this adverse effect given that repeat vaccination against COVID-19 may be

required on an ongoing basis. Symptoms may be confused with general post vaccination side effects; therefore, vigilance is needed. Subacute thyroiditis is usually straightforward to manage with symptomatic treatment with NSAIDs, beta-blockers and corticosteroids if required. A conservative approach could be considered to manage the hypothyroid phase if it is transient, as demonstrated by our case, with patient preference to avoid levothyroxine replacement. However careful monitoring of symptoms and thyroid function is required if this option is chosen. Adverse effects such as thyroiditis should not dissuade the use of vaccinations at a population level. Whether in time we will be able to identify patients who are at higher risk of developing thyroiditis remain to be seen. In the meantime, knowledge of this potential consequence will lead to earlier diagnosis and appropriate management as we continue to battle the COVID-19 pandemic worldwide.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This study did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent
Written informed consent for publication of their clinical details was obtained from the patient.

Author contribution statement
C Casey is the primary author of this case report and literature review, is an endocrinology trainee involved in the management of this patient's condition. T Higgins is the endocrinologist in charge of this patient's care.

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Received in final form 17 June 2022
Accepted 17 August 2022