

Post-COVID-19 Vaccination and Thyrotoxicosis (ASIA Syndrome): Single-Centre Experience from India with Review of Literature

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Abstract

Introduction: Thyrotoxicosis is not uncommon after immunization. It is known as ‘autoimmune/autoinflammatory syndrome by adjuvants (ASIA syndrome)’ and is caused by immunological reaction to adjuvants. However, there is insufficient information on thyrotoxicosis after COVID-19 vaccination in the Indian subcontinent. **Aims/Objectives:** To investigate the spectrum of thyrotoxicosis after COVID-19 immunization. **Settings and Design:** A single-centre retrospective study was conducted at a tertiary care academic institute in India. **Materials and Methods:** We studied the clinical symptoms, biochemical markers, imaging characteristics and treatment of every patient who was diagnosed with thyrotoxicosis within 60 days of receiving the COVID-19 vaccine. **Results:** Following COVID-19 vaccination, we diagnosed ten people (mean age 39.9 years, range 22-63 years) with thyrotoxicosis [Graves’ disease (GD, *n*-6) and subacute thyroiditis (SAT, *n*-4)]. The typical duration for symptoms to appear was 2 to 60 days. The majority of patients (*n*-9) received the COVISHIELD™ vaccine, whereas only one received the COVAXIN® vaccine. After vaccination, two patients with GD developed mildly severe Graves’ orbitopathy, with symptoms emerging two days and sixty days later, respectively. Anti-thyroid drugs (methimazole or carbimazole) were required for all GD patients. All SAT patients were treated conservatively with nonsteroidal anti-inflammatory medications and had positive outcomes. **Conclusions:** SAT, GD and GO may occur as a manifestation of ASIA syndrome, following immunization with COVISHIELD™ and COVAXIN®. Despite the obvious benefits of the COVID-19 vaccine, clinicians should be aware of any potential autoimmune and inflammatory thyroid problems.

Keywords: ASIA syndrome, autoimmune/autoinflammatory syndrome by adjuvants, COVID-19, Graves’ disease, subacute thyroiditis, thyrotoxicosis, vaccination

INTRODUCTION

Adjuvants are a class of pharmaceutical agents that are used to boost the immune response to vaccination. Paradoxically, they may also trigger an exaggerated immune response, resulting in a group of disorders known as autoimmune/inflammatory syndrome induced by adjuvants (ASIA syndrome).^[1] Among various disorders reported in the literature in ASIA syndrome, autoimmune thyroid disorders following vaccination with HBV, HPV and influenza vaccine have also been reported.^[2] Recently, thyroid disorders following COVID-19 vaccination have also been reported infrequently.^[3-18] Herein, we describe a case series of patients diagnosed with Graves’ disease (GD), Graves’ orbitopathy (GO) and subacute thyroiditis (SAT) shortly after receiving COVID-19 vaccine. Additionally, we review the cases reported in the literature so far.

MATERIALS AND METHODS

All the subjects who had presented and followed up in our department with diagnosis of thyrotoxicosis were included in our study. All those developed symptoms and signs of thyrotoxicosis within 60 days of receiving the COVID-19 vaccine^[19] were studied retrospectively. Although we did not study any patients with hypothyroidism, they would have

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been technically considered a part of ASIA syndrome as well. The study protocol was approved by the Institutional Ethics Committee. A thorough clinical history was taken, with particular attention paid to the date of COVID-19 immunization, its temporal relationship to the beginning of thyrotoxic symptoms, history of neck pain, history of fever, the presence of goitre, and signs and symptoms of GO.

In addition to the standard biochemistry tests, the following investigations were documented for the purpose of this study: total T4, total T3, free T4, TSH, anti-thyroid receptor antibody (TRAb), anti-thyroid peroxidase antibody (TPO), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ^{99m}Tc-thyroid scintigraphy (^{99m}Tc), fine needle aspiration cytology (FNAC) and high-resolution thyroid ultrasound.

In all the patients with GD, we recorded the dose and duration of anti-thyroid drugs and beta-blockers; serial thyroid function tests on treatment; and clinical activity score and history of glucocorticoids use (with dose and duration) in patients with GO. In all patients with SAT, history of use of non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (with dose and duration) was recorded.

Ethical Clearance Statement

The study protocol was approved by the Exp 45th Institutional Ethics Committee approved the study (Letter no- PGI/BE/153/2022, IEC code: 2022-21-DM). Written informed consent was obtained from all participants involved in this study, explicitly granting permission for the use of their anonymized patient data for research and educational purposes. The procedures followed throughout this study strictly adhere to the ethical guidelines set forth in the Declaration of Helsinki (2013).

RESULTS

We diagnosed ten subjects (males four, females six, mean age: 39.9 years, range: 22–63 years) with thyrotoxicosis following COVID-19 vaccination [Table 1]. These patients were found to have been immunized with either of the two COVID-19 vaccines: COVISHIELD™ (Adenovirus vectored SII-ChAdOx1 nCoV-19) manufactured by Serum Institute of India Pvt Ltd, Pune, India, and COVAXIN® [BBV152, Whole Virion, Inactivated SARS-CoV-2 virus strain (NIV-2020-770)] manufactured by Bharat Biotech International, Hyderabad, India.^[20,21] The majority of patients were vaccinated with COVISHIELD™ (*n*-9) vaccine while only one patient was given COVAXIN® vaccine. The mean period of onset of symptoms was 32 days (range: 2 to 60 days). GD was reported in six subjects (four women and two men), while SAT was diagnosed in four patients. GO was seen in two out of the six patients with GD. One patient developed ocular symptoms after 2 days and the other after approximately 1 month of vaccination. The former of the two patients was a diagnosed case of Hashimoto's thyroiditis (HT, TPO positive, baseline TSH-17) and was on thyroxine replacement prior to vaccination. Both GO patients had mild inactive

disease (EUGOGO severity scale, clinical activity score of less than 3/7). One of them even received short-term glucocorticoid treatment from their primary care physician before being referred to our institution, while the other was managed conservatively in our institute. All subjects with GD were treated with anti-thyroid drugs (carbimazole) along with beta-blockers while subjects with SAT were treated with NSAIDs and beta-blockers. All the SAT patients showed resolution of symptoms without the requirement of glucocorticoids during the course of their illness.

DISCUSSION

Worldwide, the coronavirus illness (COVID-19) has significantly increased morbidity and mortality. Following COVID-19 infection, endocrinopathies including autoimmune diabetes, premature ovarian failure and adrenal insufficiency have all been documented in the literature.^[22] In contrast to the enormous population affected globally, GD and SAT have been reported less frequently than other endocrine disorders. The pathogenesis of these disorders has been suggested to be caused by the virus itself or a dysregulated immune response. The first hypothesis was advanced in light of the knowledge that COVID-19 is known to enter its host cell with the aid of the angiotensin-converting enzyme (ACE2) receptor, which is widely located in several endocrine organs, including the thyroid gland.^[23] The latter theory was reached in light of the possibility that COVID-19 could exacerbate latent autoimmunity, which could then result in the development of GD, GO, postpartum thyroiditis, or Hashimoto's thyroiditis.^[24]

In order to prevent as well as lessen the severity of disease, COVID-19 vaccines were developed. They were developed using traditional platforms such as inactivated whole virus (COVAXIN® and Coronavac vaccine) and newer platforms such as protein subunit (COVOVAX™, CORBEVAX®), adenoviral-vectored (Johnson and Johnson vaccine, Oxford-Astra Zeneca, COVISHIELD™, VAXZEVRIA®), mRNA-based (Moderna and Pfizer-BioNTech COMIRNATY®) and DNA (ZyCoV-D). These vaccines contain excipients such as aluminium hydroxide or aluminium salts (Coronavac vaccine), polysorbate 80 (Astra-Zeneca vaccine) or polyethylene glycol lipid conjugates that stabilise the lipid nanoparticles in mRNA vaccine (Pfizer BioNTech). These adjuvants enhance the immunogenicity of these vaccines by increasing both innate and adaptive immune responses.

The adjuvants act by mimicking evolutionary conserved foreign chemicals, such as bacterial cell walls and lipopolysaccharides, and subsequently bind to toll-like receptors (TLRs) found on immune cells, thus enhancing the body's immune response. In addition to molecular mimicry, they can also activate the NALP3 inflammasome system within the cell and directly promote the activity of immune cells. With the increased release of chemokines and cytokines from T cells and mast cells, all of this leads to an increased local response to antigens.^[25,26]

Table 1: Summary of baseline characteristics and laboratory and imaging tests of each patient

Sex/ Age	Type of vaccine	Time to symptoms onset	Baseline thyroid function tests	TPO(<35)/ TRAb (<1.75)	ESR/ CRP	⁹⁹ Tc Thyroid Scan	Diagnosis
43/F	adenoviral-vectored	2 days	TSH 0.11, TT3-188 ng/dl (60-180) TT4-14.6 ug/dl (5-12.4)	1300/28.5	77	Diffuse uptake both lobes	Mild GO Inactive
24/M	adenoviral-vectored	60 days	TSH- <0.005, TT3-16 pg/ml (2.3-4.0) TT4-3 ng/dl (0.8-1.7)	329/5.5	40/30	Diffuse uptake both lobes	Mild GO inactive
63/M	adenoviral-vectored	60 days	TSH- 0.005, TT3-8.3 nmol/l (1.3-3.1) TT4-261 nmol/l (58-162)	22.7/38.27	20/2	Diffuse uptake both lobes	GD
22/F	adenoviral-vectored	30 days	TSH- 0.01, FT3-6.3 pg/ml (2.3-4.2) FT4-3.5 ng/dl (0.8-2.7)	--/17.2	20/8	Diffuse toxic goiter	GD
44/F	adenoviral-vectored	30 days	TSH-0.2, T4-14.5 ug/dl (5-14) T3-4 ng/ml (0.8-2)	144/34.5	16/25	--	GD
25/F	adenoviral-vectored	10 days	TSH- <0.01, TT3-400 ng/dl (60-180) TT4-23 ug/dl (0.55-4.8)	>1000/>40	-	Diffuse toxic goitre	GD
49/M	adenoviral-vectored	60 days	TSH- 0.005, TT3-3 ng/ml (0.6-1.8) TT4-18 ug/ml (5-12.4)	96/--	-	Gland not visualized	SAT
46/M	Inactivated Whole virus	30 days	TSH- 0.01, FT3-8.1 pg/ml (2.3-4.3) FT4-3.6 ng/dl (0.9-1.7)	33/<1.75	85/118	Gland not visualized	SAT
51/M	adenoviral-vectored	20 days	TSH-<0.01 TT3-2.43 nmol/l (1.3-3.1) TT4-12.7 (58-162)	--	-	Gland not visualized	SAT
32/M	adenoviral-vectored	18 days	TSH-<0.014, T3-2.2 nmol/l (1.3-3.1) T4-164 nmol/l (58-162)	424/<0.8	-	Normal size and Function	SAT

F=Female, M=Male, CAS=Clinical activity score, TT3=Total T3, TT4=Total T4, FT3=Free T3, FT4=Free T4, TSH=Thyroid stimulating hormone, TRAb=TSH receptor antibody, TPO=Anti-thyroid peroxidase antibody, ESR=Erythrocyte sedimentation rate, CRP=C-reactive protein, ⁹⁹Tc=Technetium 99, GD=Graves' disease, SAT=Subacute thyroiditis

While these adjuvants are beneficial in stimulating the body's immunity to subsequent infection, they are also known to exaggerate immune response in certain genetically susceptible individuals, leading to a group of disorders known as the autoimmune/autoinflammatory syndrome by adjuvants (ASIA syndrome).^[26] The phrase 'ASIA syndrome' was first coined in 2011. Initially, only four disorders were included under the umbrella of ASIA syndrome: Siliconosis, Gulf War syndrome, macrophagic myofasciitis syndrome and post-vaccination disorder.^[1] Subsequently, the syndrome was broadened to include a variety of autoimmune and autoinflammatory disorders.^[27] Hepatitis B, Human papillomavirus, and influenza vaccines have all been linked to ASIA syndrome. In the literature, adjuvants such as aluminium hydroxide, silicone implants and mineral oil fillers have been blamed for post-vaccination ASIA syndrome.^[28] Autoimmune endocrine diseases such as type 1 diabetes mellitus, primary ovarian failure, adrenal insufficiency and autoimmune thyroid diseases have been reported to be related

to ASIA syndrome after human papillomavirus, influenza and hepatitis B vaccination.^[2]

Despite the fact that ASIA syndrome has been known about for more than ten years, little is known about it. This is especially true for endocrine disorders following COVID-19 vaccination which is a relatively new discovery. A number of autoimmune thyroid disorders have been reported following COVID-19 vaccination. SAT has been described following administration of inactivated whole virus,^[3,4,11,12] adenoviral-vectored^[14-16] and mRNA-based vaccines.^[16] Silent thyroiditis has also been reported with mRNA vaccines.^[5] Similarly, GD has also been reported following adenoviral-vectored^[6,7,13] and mRNA-based vaccines.^[5,8,9,17,18,29] Recurrence of GD has also been reported following the mRNA vaccine.^[7,9,13,18] A recent systematic review described 52 cases of SAT, 31 cases of GD and 6 cases of silent autoimmune thyroiditis after COVID-19 vaccination. The mean time to symptoms onset was reported to be 1–21 days in SAT and 1–60 days in GD patients.^[19] Another review reported 98 cases of SAT, 79 cases of GD, 24 cases

Table 2: Summary of published cases of thyrotoxicosis following COVID-19 vaccination.

Author	Sex/Age	Onset after vaccination	Vaccine type	Investigations	USG thyroid and Tc-99 scan
Sub-acute thyroiditis					
Iremli (3)	35/F	4 days	Inactivated whole virus	TPOAb- Negative TRAb- Negative ESR/CRP-53/100	Bilateral focal hypoechoic areas with decreased blood flow
Iremli (3)	34/F	4 days	Inactivated whole virus	TPOAb- Negative TRAb- Negative ESR/CRP-9/6	Bilateral focal hypoechoic areas with decreased blood flow
Iremli (3)	37/F	7 days	Inactivated whole virus	TPOAb- Negative TRAb- Negative ESR/CRP- 25/2.4	Bilateral focal hypoechoic areas with decreased blood flow
Şahin (4)	67/M	14 days	Inactivated whole virus	TPOAb- Negative TRAb- Negative ESR-67 (<10) CRP-54(<5)	Reduced echogenicity and diffusely heterogeneous
Soltanpoor (11)	34/F	5-7 days	Inactivated whole virus	ESR-60 CRP-9.8	Heterogeneous echogenicity, decreased vascularity, decreased uptake
Saygili (12)	38/F	2 weeks	Inactivated whole virus	TPOAb- Negative ESR- 78 CRP-8.7 (<20)	Irregularly enlarged hypoechogenic
Lee (13)	39/F	4 days	Adenovirus Vectored	TPOAb- <15 (<34) TRAb- <1.1 (<1.75) ESR/CRP-63/28.6	Increased vascularity, decreased uptake
Lee (13)	73/F	11 days	Adenovirus Vectored	TPOAb<15 (<34) TRAb- 1.4 (<1.75) ESR/CRP-85/34.6	Ill-defined hypoechoic lesions
Lee (13)	33/M	10 days	Adenovirus Vectored	TPOAb<15 (<34) TRAb<1.1 (<1.75) ESR/CRP-37/5.16	Heterogeneous echogenicity, decreased vascularity, decreased uptake
Das (14)	47/F	2 weeks	Adenovirus Vectored	TPOAb- 11.8 (<34) TRAb- 1.3 (<1.75) ESR/CRP-60/9.8	Bulky thyroid with hypoechoic nodules, No uptake
Oyibo (15)	55/F	3 weeks	Adenovirus Vectored	TRAb- Negative ESR/CRP-51/87	Heterogeneous echogenicity
Bornemann (16)	26/F	2 weeks	Adenovirus Vectored	TPOAb- Negative TRAb- Negative CRP-14.3	Heterogeneous echogenicity, decreased vascularity
Bornemann (16)	49/F	3 weeks	mRNA	TPOAb- Negative TRAb- Negative CRP-21.9	Heterogeneous echogenicity, decreased vascularity
Graves' disease					
Lee (13)	46/F	1 day	Adenovirus vectored	TPOAb-77.7 (<34) TRAb- 6.4 (<1.75) ESR/CRP-5/0.05	Increased vascularity, diffuse hypoechogenicity, increased vascularity, increased uptake
Lee (13)	73/F	14 days	Adenovirus Vectored	TPOAb-41 (<34) TRAb- 6.3 (<1.75)	Increased vascularity, increased uptake (54%)
Lee (13)	34/M	Recurrence 14 days	Adenovirus vectored	TRAb- 4.2 (<1.75)	Increased vascularity
Lee (13)	39/M	Concurrent GD and SAT 14 days	Adenovirus Vectored	TPOAb<15 (<34) TRAb- 2.9 (<1.75) ESR/CRP-74/36.5	Diffuse goitre ill-defined hypoechoic lesion in left, increased uptake (13.8%)
Vera Lastra (17)	40/F	2 days	mRNA	TRAb- Positive	Enlargement and hypervascularity
Vera-Lastra (17)	28/F	3 days	mRNA	TRAb- Positive	Enlargement and hypervascularity, diffuse uptake

Contd...

Table 2: Contd...

Author	Sex/Age	Onset after vaccination	Vaccine type	Investigations	USG thyroid and Tc-99 scan
Graves' disease					
Zettinig (18)	71/F	Recurrent/ 56 days	mRNA	TRAb- Positive	Multiple anechogenic areas, increased vascularisation, patchy tracer distribution, increased uptake
Zettinig (18)	46/M	15 days	mRNA	TRAb- Positive	Slightly enlarged, hypo and anechogenic areas, increased vascularity, patchy tracer distribution, normal uptake
Pujol (5)	38/F	12 days	mRNA	TRAb- Positive	Diffuse hypoechoic, increased vascularity
Sriprapradang (6)	70/M	2 days	Adenovirus Vectored	TRAb- 3.23 (< 1.75) CRP- 1 (<3)	N/A
Sriprapradang (7)	30/F	Recurrence/4 days	Adenovirus Vectored	TRAb- 13.4 (<1.75)	N/A
Patrizio (8)	52/M	28 days	mRNA	TRAb- 6.48 (<1.5) TPOAb- 21 (<10)	Enlarged heterogeneous echotexture, increased vascularity
Pierman (9)	34/F	Recurrence/10 days	mRNA	TRAb- positive	N/A
Pla Peris (10)	71/F	60 days	mRNA	TRAb-positive	Enlarged thyroid, increased vascularity, diffuse increased uptake
Pla Peris (10)	42/F	<14 days	mRNA	TRAb-positive	Enlarged thyroid, increased vascularity, diffuse increased uptake
Pla Peris (10)	54/F	<14 days	mRNA	TRAb-positive	Enlarged thyroid, increased vascularity
Pla Peris (10)	46/F	50 days	mRNA	TRAb-positive	Enlarged thyroid, increased vascularity
Pla Peris (10)	69/F	<14 days	mRNA	TRAb-positive	Enlarged thyroid gland, heterogeneous echogenicity, diffuse hypochoic pattern

F=Female, M=Male, CAS=Clinical activity score (EUGOGO guidelines), TT3=Total T3, TT4=Total T4, FT3=Free T3, FT4=Free T4, TSH=Thyroid stimulating hormone, TRAb=TSH receptor antibody, TPO=Anti-thyroid peroxidase antibody, ESR=Erythrocyte sedimentation rate, CRP=C-reactive protein, ⁹⁹Tc=Technetium 99

of GO and seven cases of silent thyroiditis after COVID-19 vaccination. The mean time to symptoms onset was reported to be 1–84 days in SAT, 1–63 days in GD patients and 10–21 days in silent thyroiditis.^[30]

Vast majority of the cases were reported after mRNA and inactivated whole virus-based vaccines. These were reported after the first dose, the second dose and even the booster dose.^[9,19] Salient features of some of the cases from the literature have been shown in Table 2. Similar to the above findings, thyroid disorders were more commonly reported after the adenovirus vector-based vaccine (COVISHIELD™) compared to the inactivated virus vaccine (COVAXIN™) in our study. No patient in our study received mRNA vaccine. Among several explanations for such a finding (variable used doses, humoral-mediated and cell-mediated immunity response), one may be that mRNA and adenovirus-vectored type vaccines have higher immunogenicity than inactivated SARS-CoV-2 vaccine.^[31]

The pathogenesis of SAT or GD post-vaccination is considered to be multifactorial. Vaccine adjuvants may play a role in triggering a variety of autoimmune and inflammatory responses. Cross-reactivity between the coronavirus spike protein target produced by the mRNA vaccination and antigens found in healthy thyroid cells has also been discussed.^[5,17] One study also suggested the role of certain HLA alleles in the pathogenesis of post-vaccination SAT.^[32] The interplay

between genetic predisposition, a history of other autoimmune disorders, adjuvants and cross-reactivity between spike proteins and healthy thyroid cell antigens all needs to be investigated further.

Compared to the millions of people who have received COVID-19 immunization, cases of clinically evident thyroid dysfunction have been recorded only sparingly. This could be due to underreporting, low rate of post-vaccination adverse events or a lack of awareness among clinicians in general.

The strengths of our study are that all patients were extensively evaluated and one of the patients even had thyroid function tests (TFTs) suggestive of Hashimoto's thyroiditis prior to vaccination. It is also one of the largest case series reported on this topic from India.

The limitations of our investigation include the retrospective design and the absence of TFTs and autoantibody titres prior to COVID-19 vaccination for all the patients. It should also be noted that this could be a random event observed after vaccination, albeit the only way to confirm this is through an animal model. Another drawback of our study would have been missing all cases that occurred after 60 days of vaccination [cut-off taken at the time of writing the protocol,^[19] as cases up to 84 days of vaccination have been reported in studies subsequently. We also did not study cases of hypothyroidism as part of our study which might have limited the number of cases of ASIA

syndrome in our study. A multicentre prospective study with thyroid function and auto-antibody titres prior to and after COVID-19 vaccination might help understand this problem better. Our case series serves as a reminder to clinicians that COVID-19 vaccination might cause thyrotoxicosis.

CONCLUSION

SAT, GD and GO may occur as a manifestation of ASIA syndrome, following immunization with COVISHIELD™ and COVAXIN®. In light of this knowledge, clinicians should be aware of the risk of development of GD and SAT following COVID-19 vaccination.

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Conflicts of interest

There are no conflicts of interest.

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