



## Post-COVID-vaccine autoimmune/inflammatory syndrome in response to adjuvants (ASIA syndrome) manifesting as subacute thyroiditis

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SAT is a common thyroid-related syndrome in COVID-19 [1]. However, SAT following vaccine for SARS-CoV-2 is rare. Herein, we report the case of a 47-year-old female who presented with fever and neck pain for 2 weeks following the first dose of the ChAdOx1 nCoV-19 (Astra Zeneca) vaccine. The fever was moderate-to-high grade, continuous, and associated with neck pain radiating to the jaw. She also complained of restlessness, difficulty in swallowing and weight loss of 3 kg in this duration. She was febrile and had tachycardia (110/min). Her neck examination showed a tender goitre (WHO grade II) with no palpable lymphadenopathy. Thyroid function tests (TFT) revealed thyrotoxicosis (T3 2.2 ng/ml [N 0.8–2 ng/ml], T4 12.9 µg/dl [N 4–12 µg/dl], TSH 0.06 µIU/ml [N 0.2–4.2µIU/ml]). Thyroid antibodies (antiTPO 11.8 IU/ml [N < 34] and TRAb 1.28 IU/ml [N < 1.75]) were normal. Neck ultrasound showed a bulky thyroid with hypoechoic nodules (1.5 × 1.0 cm in the right and 0.8 × 0.5 cm in the left lobe) without any cystic changes, calcification or increased vascularity. She underwent a pertechnetate (<sup>99m</sup>Tc–TcO<sub>4</sub><sup>-</sup>) thyroid scan, which revealed no tracer uptake in the thyroid gland (Fig. 1A). Fine-needle aspiration cytology of the right-sided suspicious nodule showed granulomatous inflammation. The patient was diagnosed with SAT and advised 40 mg propranolol daily. She showed a gradual improvement in her restlessness and gained weight, besides having resolution of her neck discomfort. On re-evaluation after 8 weeks, she had complete resolution of her presenting features, with normal

TFT (T3 1.09 ng/ml, T4 7.04 µg/dl, and TSH 1.50 µIU/ml). Repeat scan showed improved trapping function (Fig. 1B). The index case depicts a classic case of autoimmune/inflammatory syndrome in response to adjuvants (ASIA syndrome) in a recipient of SARS-CoV-2 following the first dose of the COVID vaccine.

ASIA syndrome is an entity first described in 2011 by Schoenfeld [2]. Adjuvants are used to enhance the immunogenicity of vaccines, to increase both innate and adaptive immune responses. However, as a bystander phenomenon, vaccine adjuvants can induce the formation of autoantibodies or inflammation (localised or systemic), which may manifest as autoimmune/inflammatory syndromes. Though systemic inflammatory conditions are common, autoimmune thyroid disease as part of ASIA syndrome is uncommon, despite it being the most common autoimmune endocrinopathy. There are a few reports of Graves' disease, Hashimoto's thyroiditis and subacute thyroiditis (SAT) reported after the first or second dose of vaccines [3, 4].

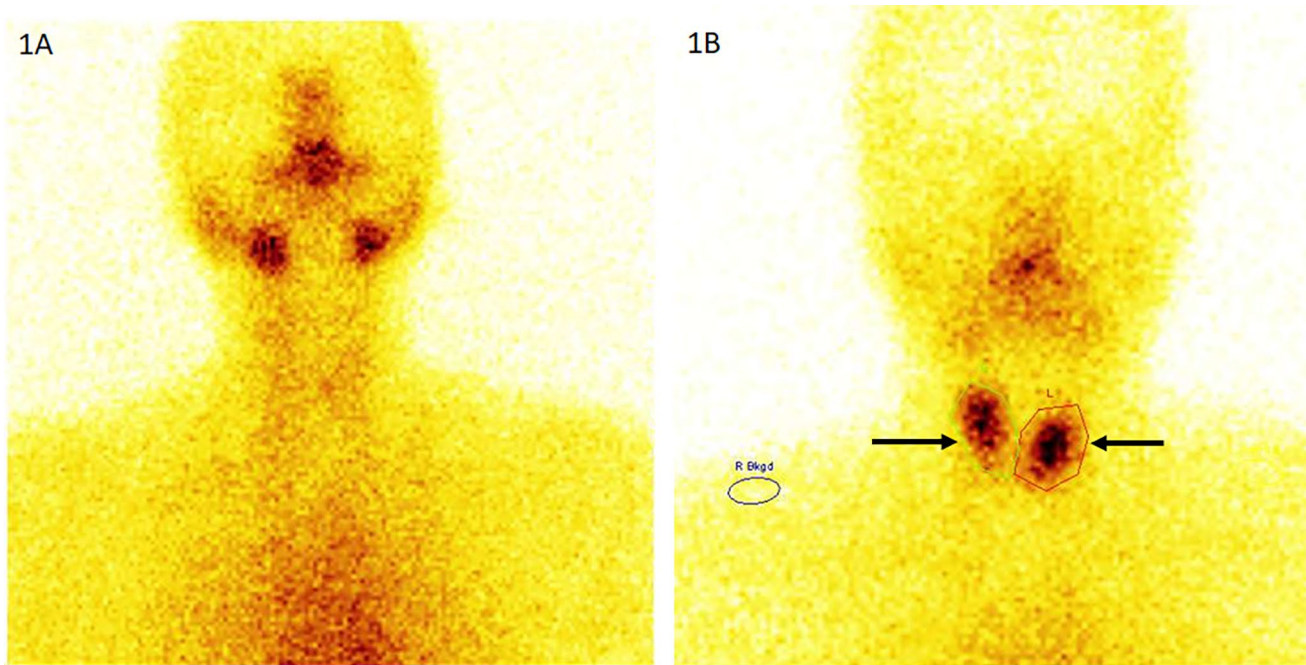
SAT as part of ASIA syndrome is previously reported with hepatitis B, HPV and influenza vaccinations. There are very few instances of SAT following administration of COVID vaccines, and some prior reports have been confounded by concurrent presence of other factors that may be contributory for the development of SAT, such as post-partum period [5–7] (Table 1). All reported cases are females, except one [6]. ASIA has been reported as early as 3–5 days following the vaccine, until as late as 21 days, and most commonly following the first dose. However, scintigraphic evidence of SAT in a recipient of the first dose of the ChAdOx1 nCoV-19 vaccine has never been hitherto demonstrated.

The index case suggests harbouring a high index of suspicion in recipients of the vaccine. Masking of symptoms, self-limiting nature and under-recognition may be the reasons for the very few reports of ASIA syndrome following

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**Fig. 1** XXX

**Table 1** Review of literature of cases of subacute thyroiditis as part of autoimmune/inflammatory syndrome in response to adjuvants (ASIA syndrome)

Author	Age/Gender	Type of vaccine	Dose	Lag period of symptom onset	Ultrasonogram thyroid	<sup>99m</sup> Tc TcO <sub>4</sub> <sup>-</sup>	Additional therapy/Recovery duration
Iremli et al.	35/F 34/F 37/F	Sinovac (Vero cell inactivated whole virus) Aluminium hydroxide adjuvant	2nd dose, 1st dose, 2nd dose	4–7 days	Bilateral focal hypoechoic areas Bilateral focal hypoechoic areas Bilateral focal hypoechoic areas	ND	Methylprednisolone, propranolol/ 4 weeks Methylprednisolone, propranolol/ 10 weeks No treatment/8 weeks
Oyibo et al.	55/F	Astra-Zeneca (adenovirus spike protein component vaccine)	2nd dose	21 days	Enlarged heterogeneous echotexture	ND	Propranolol, NSAIDs LT4 therapy required in follow-up/ 12 weeks
Sahin Tekin et al.	67/M	Vero-cell inactivated whole virus	2nd dose	10–12 days	Enlarged heterogeneous, hypoechoic pseudonodules	ND	No additional therapy/8 weeks
Current	47/F	Astra Zeneca (adenovirus spike protein component vaccine)	1st dose	21 days	Enlarged gland, heterogeneous echotexture, hypoechoic nodules	Absent technetium uptake on the initial scan followed by normal uptake (1%) 8 weeks later	No specific therapy/8 weeks

COVID vaccine. Though heterogeneous echotexture is the most common pattern in SAT following COVID vaccination,

the index case had nodules in the presence of biochemically and scintigraphically confirmed SAT. The fact that TFT

normalised, while thyroid scan was still improving is in line with the natural history of SAT [8]. Thyrotoxicosis temporally associated with the first dose of vaccine, scintigraphic evidence of absent uptake, with following of normalisation of symptoms, TFT and resolving uptake at 8 weeks from initial onset of disease, suggests the diagnosis of SAT due to ASIA syndrome. Probable mechanisms include the activation of autoimmune cascades, polyclonal activation of B-lymphocytes and molecular mimicry. ACE2 receptor-mediated mechanism is also plausible considering the fact that the ChAdOx1 nCoV-19 is a simian-virus vectored spike protein of SARS-CoV-2 which in fact binds to ACE2 and the thyroid is known to have one of the highest expression of ACE2 in follicular cells [9, 10].

Our case is the first case of COVID-19 vaccine-related SAT with nodular goitre proven by scintigraphic evidence at diagnosis and during recovery. Though the case represents a rare adverse inflammatory endocrinopathy following COVID vaccine, this should not deter the use of vaccination, as it can be timely diagnosed and effectively managed.

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## Declarations

**Conflict of interest** The authors have no conflicts of interest to declare.

**Research involving human participants and/or animals** All procedures performed were in accordance with the ethical standards of the institutional and/or research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethical committee approval is not required for case reports.

**Informed consent** Written, informed consent was obtained from the patient for participation and publication.

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