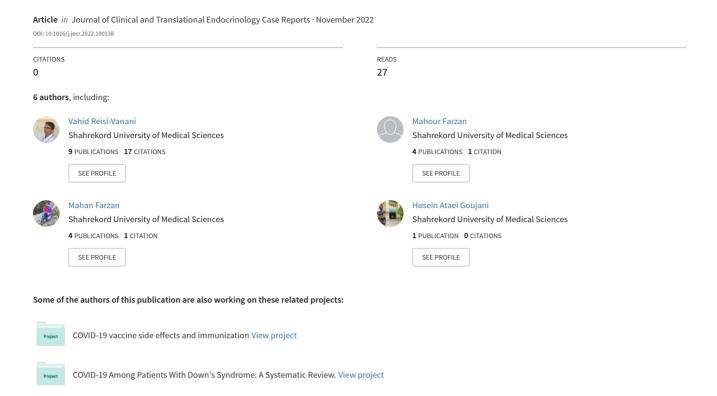
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Role of the immune system and possible mechanisms in COVID-19 vaccine-induced thyroiditis: Case report and literature review

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ABSTRACT

Introduction: Subacute thyroiditis (SAT) is an inflammatory disease that has different trigger factors. Recent studies show the possible role of COVID-19 vaccine-induced thyroiditis in its initiation. Herein we report the first case of post-Sputnik V vaccination SAT.

Case presentation: A 42-year-old man without any specific disease was admitted due to tremors, palpation and sweating, and neck tenderness on the thyroid gland. Laboratory markers and radiologic assessments highlighted thyroiditis for him, and his symptoms were relieved by administering NSAIDs and corticosteroids.

Discussion: There are several hypotheses for the etiology of post-COVID-19 immunization SAT; among them, immunologic reactions like the interactivity of human proteome with viral components and autoimmune/inflammatory syndrome induced by adjuvants (ASIA) are more probable than other discussed possibilities. We suggest further studies to discover the exact SAT pathophysiology to prevent the underlying causes among future vaccine candidates.

1. Introduction

Subacute thyroiditis (SAT) is a rare inflammatory disorder that causes symptoms like thyrotoxicosis and throat tenderness. It usually occurs 1-2 weeks following viral infection. Difficulties in SAT diagnosis are due to its nonspecific clinical symptoms and self-limiting feature [1]. Patients with SAT can develop symptoms of hyperthyroidism, hypothyroidism, and complete recovery may even last several months. Untreated SATs can precede permanent complications. Since SAT is strongly associated with viral infections, an increase in SAT incidence seems possible during this COVID-19 pandemia [2]. Viruses are the leading cause of this condition, and adenovirus, enterovirus, coxsackievirus, mumps, measles, and recently coronaviruses had been reported to cause thyroiditis as thyroid cells could express angiotensin-converting enzyme-2 (ACE-2) receptors that might facilitate direct invasion of coronavirus to it [3]. To our knowledge, there are few reported cases of SAT following Sputnik V vaccination, and a review of literature on post-COVID-19 immunization SAT.

2. Case presentation

A 42-year-old man presented to the clinic with neck pain and swelling, difficulty in swallowing, occasional hot flashes, palpitation, tremors, fatigue, and malaise. He got the first dose of COVID-19 Sputnik V seven days before the initiation of his symptoms: He also did not have any past medical history and was infected with severe acute respiratory syndrome coronavirus 2 six months ago that was treated in outpatient settings. After the first dose administration, he felt symptoms like fatigue, fever and chills, sore throat, and myalgia persisting for about two days. Due to the COVID-19 pandemia, COVID-19 RT-PCR was done with a negative result for this virus and had tried to treat his symptoms with antihistamines and antibiotics without any consultation with a physician. Since his symptoms did not get better, he presented to a clinic 20 days after the initiation of symptoms. He also refused to inject the second dose of the vaccine. Since he had been participating in a study investigating post-vaccination antibody response (Ethic code: IR. SKUMS.REC.1400.090), his serum had been collected and stored before injection of the first vaccine dose. Sample analysis after the diagnosis of

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Table 1
Laboratory data of patient. First, second and third blood sample were gathered before vaccine injection, 23 days, and six month after the only vaccine dose.

Test	1st sample	2nd sample	3rd sample	Reference
Т3	1.43	3.99	1.51	1.3–3.4 nmol/L
T4	83	271.6	88	66-180 nmol/L
TSH	5.18	0.1	3.50	0.25-5 mIU/mL
Anti-TPO	11.5		14.4	Positive: >40 IU/mL
Anti-TG	13.2		13.5	Normal: < 115 IU/mL
Anti-Spike antibody	26.3		100≥	Positive: ≥ 8
				RU/mL
				Negative: <8
WBC		12300		4000-12000
Neutrophil		8856		
Lymphocyte		2091		
Mix%		1353		
ESR 1h		71		Normal: <15
CRP		++		

T3 Triiodothyronine, T4 thyroxine, T5H thyroid-stimulating hormone, Anti-TPO Anti-thyroid Peroxidase Antibody, Anti-TG Antithyroglobulin antibody, WBC white blood cells, E5R erythrocyte sedimentation rate, CRP C-reactive protein.

SAT revealed subclinical hypothyroidism for him before the administration of the vaccine. Because of his clinical signs and symptoms like neck tenderness on the thyroid gland, sweating, tremor, and palpation, laboratory (Table 1) and radiological assessments were conducted for him, including thyroid function tests and thyroid ultrasound. Thyroid ultrasound showed mild enlargement of the thyroid gland with hypoechoic and heterogenic parenchyma in favor of acute thyroiditis. The radiologist also reported a hyper echo, well-defined solid nodule about 5.5 mm² in the upper part of the left lobe. Naproxen 750 mg/day and prednisolone 12 mg/day was prescribed for him for one week and was tapered in 4 weeks. As his thyroid function tests were in their normal range, levothyroxine had not been prescribed, and he did not use betablockers for his symptoms in the course of his disease.

3. Discussion

Subacute thyroiditis is a transient inflammation of the thyroid gland that occurs about 12/10000 per year in the United States. Its absolute etiology is still unknown, but epidemiological studies suggest an association between viral infections and its occurrence. Thyrotoxicosis symptoms besides neck tenderness and thyroid gland enlargement direct physicians to this diagnosis. Although a transient increase in anti-TPO antibody titer might occur during its course, other anti-thyroid antibodies are usually absent in this disease, and physicians screen TSH, fT4 (and sometimes fT3) in suspected patients [4]. Besides its self-limiting characteristic, some life-threatening adverse events especially due to thyrotoxicosis, including cardiac arrhythmias could occur, making its diagnosis, treatment, and follow-up important [5].

SAT occurrence after the COVID-19 infection made researchers mention the coronavirus in the group of viruses that could trigger SAT [6]. There are many theories about its etiology including: the direct invasion of the virus to the thyroid cells through ACE-2 and transmembrane protease serine 2 (TMPRSS2) receptors, inflammatory mechanisms, and even autoimmunity with viral components mimicking human proteome [7]. Besides COVID-19 infection, its vaccine can also be associated with SAT with several possible mechanisms. Autoimmune and immune-mediated reactions are one of the underlying theories. Reports of autoimmune hepatitis, type 1 diabetes mellitus, and Graves' disease after COVID-19 vaccination raised the possibility of immune-mediated mechanisms [8-12]. One probable reason is the cross-reactivity of the human proteome with virus components like spike protein, nucleoprotein, and membrane protein [13] which are the main target of vaccines. Sputnik V and other similar vaccines can trigger the immune system to produce IgG₁ monoclonal antibodies against the spike of the virus that has cross-reactivity with TPO, thyroglobulin, and other

cellular components of the thyroid gland [14], structural similarities between antibodies induced by vaccine and human tissue antigens are demonstrated in a study [15], that might be the triggering point for post-vaccination autoimmunity. The presented case was infected with COVID-19, and his anti-spike antibody titer was positive before vaccination. Although he had injected just the first dose of vaccine, his high antibody titer could explain somehow the relationship between vaccine-induced antibody and following SAT.

Another immune-mediated reaction that can induce autoimmune disease, especially endocrinopathies, is autoimmune/inflammatory syndrome induced by adjuvants (ASIA). Many autoimmune disorders have been reported with vaccines using adjuvants in their ingredients to increase the efficacy of immunization; These substances can disturb immunoregulatory checkpoints, lead to polyclonal stimulation of B lymphocytes which affects T lymphocytes besides disturbance of regulatory cells that can trigger the production of viral-induced antibodies with the ability of binding to endogenous proteins for their molecular similarities. Hashimoto's thyroiditis, Graves' disease, primary ovarian failure, and type 1 diabetes mellitus have been reported after several vaccine adjuvants [16]. Many researchers suggest the role of ASIA in post-COVID-19 immunization thyroiditis [13,14,17] besides other endocrinopathies after vaccination like hypophysitis [18]. Although ASIA seems to justify these disturbances, many controversies about the duration of post-vaccination disease, especially in acute thyroiditis, suggest modifying the diagnosis criteria of ASIA [19] and investigating more accurate studies on it.

Recent studies show an association between SAT and the presence of HLA-B*35, HLA-B*18:01, DRB1*01, and C*04:01 which demonstrates the genetic susceptibility of patients that can also affect their duration and type of treatment [20,21]. Unlike chronic thyroiditis which involves both cellular and humoral immunity, cytotoxic T cells play a significant role in SAT pathogenesis by recognizing the viral and thyroid cell antigens and inducing transient inflammation [22].

There are many reports of SAT after COVID-19 immunization that usually occurred 4–7 days after the injection, as is demonstrated in Table 2 [13] which is consistent with our case and would help its diagnosis if physicians know the characteristic of post-vaccination thyroiditis.

Discussing mentioned hypothesis for the etiology of post-COVID-19 immunization SAT, the possibility that the onset of SAT after the vaccine could be just a mere coincidence should be pointed out. If AISA has stronger evidence, administration of a different vaccine with different adjuvants would diminish the possibility of thyroiditis after booster doses. Finally, we suggest more studies on the underlying mechanisms.

(continued on next page)

 Table 2

 Clinical manifestation and medication of sub-acute thyroiditis followed by COVID-19 vaccination.

S*	Age/ Sex	Vaccine	PMH	vaccination to SAT	SAT sign and Symptoms	Medication	S	Age/ Sex	Vaccine	РМН	vaccination to SAT	SAT sign and Symptoms	Medication
[24]	67/ M*	CoronaVac® (Sinovac Life Sciences, Beijing)	HTN*	17 days after 2nd dose	Hypertension, Weight loss, Fever, Mild pain in anterior neck and left ear, minimal tenderness in the thyroid palpation	Lercanidipine Paracetamol ibuprofen	[23]	55/F	AstraZeneca (ChAdOx1 nCoV-19 vaccine)	well- controlled asthma	3 weeks after 1st dose	Neck pain and swelling for 4 weeks, headache, sore throat, myalgia, and palpitations	Propranolol Ibuprofen Paracetamol Levothyroxine
[26]	34/ F*	COVAXIN(The Bharat BiotechCOVID- 19Vaccine)	No PMH*	5th-7th day post vaccination	Intermittentmild fever, palpitation and radiating anterior neck pain, thyroid gland enlargement and tender	prednisolone	[25]	38/F	CoronaVac® (Sinovac Life Sciences, Beijing)	No PMH	2 weeks after the second dose	swelling in the neck, pain, fatigue, loss of appetite and sweating, stage 2 goitre, tenderness over the right thyroid lobe	Naproxen sodium Propranolol Levothyroxine
[28]	42/F	Pfizer/ BioNTech	No PMH	5 days after first dose	sore throat and palpitationsheart rate in the 130swith sinus tachycardia on EKG	Ibuprofen Prednisone Propranolol	[27]	51/F 39/F	Pfizer/ BioNTech AstraZeneca (ChAdOx1	No PMH No PMH	4 days after receiving the first dose 3 weeks	nausea, mild anterior neck pain and fever up to 38,2 °C tender	Methylprednisolone No special treatment
[29]	26/F 49/F	Vaxzervria (AstraZeneca; Sweden) Spikevax (Moderna Biotech, Spain)	No PMH Benign thyroid nodules	2 weeks after the first dose 2 weeks after the first dose	Cervical pain that radiated to both ears, fever and chills, tenderness in the thyroid Sore throat, headaches and difficulty in concentrating, right cervical pain radiating to the ear	Ibuprofen Prednisolone Ibuprofen Diclofenac Prednisolone	[30]	75/M	nCoV-19 vaccine) AstraZeneca (ChAdOx1, Vaxzervria).	No significant PMH	14 days	in thyroid gland on palpation headache, fever, neck pain and tenderness, shortness of breath, intermittent palpitations, insomnia and anxiety,	Ibuprofen
[13]	35/F 34/F 37/F	CoronaVac® (Sinovac Life Sciences, Beijing) (CoronaVac®, Sinovac Life Sciences, Beijing) (CoronaVac®.	No PMH Covid-19 No PMH	4 days after the second dose 4 days after first dose 7 days after the second dose	Severe sore throat, palpitation, fever, fatigue, sensitive, painful, and enlarged thyroid gland anterior neck pain, fatigue, weight loss, palpitations, myalgia mild anterior neck pain, mild tenderness over the	Paracetamol Methylprednisolone Propranolol Methylprednisolone Propranolol Paracetamol	[31]	57/F	Pfizer/ BioNTech	No PMH	34 days after first dose 13 days after second dose	tachycardia progressive anterior neck pain and swelling, fever (38.3), right thyroid gland enlargement with diffuse tenderness	Propranolol Ibuprofen Prednisone
		Sinovac Life Sciences, Beijing)			right lobe of the thyroid gland, palpated, sensitive and enlarged right lobe of thyroid (at 4th week)		[14]	middle- aged/F	Pfizer/ BioNTech	No PMH	2 weeks after the second dose	Poor sleep, worsening night sweats, hyper defecation, weight loss, neck pain, swelling, and tenderness	NSAID*
							[32]	46/F	Moderna mRNA-1273 SARS-CoV-2	migraine	32 days after the first dose and immediately after the second dose	A tender, swollen area with increased warmth and firm consistency was	Dexamethasone Propranolol methylprednisolone

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Table 2 (continued)

S*	Age/ Sex	Vaccine	РМН	vaccination to SAT	SAT sign and Symptoms	Medication	S	Age/ Sex	Vaccine	PMH	vaccination to SAT	SAT sign and Symptoms	Medication
[33]	42/F	Moderna mRNA COVID-19 vaccine	Colon cancer	6 days after second dose	bilateral ear pain right- sided and then left-sided earache radiating down to the lateral and anterior neck and bilateral lower jaw, ear pain was exacerbated by turning her head, swallowing, and coughing, anterior	NSAID	35	46/F 73/F 34/F 33/M	AstraZeneca AstraZeneca Janssen (Johnson & Johnson) Janssen (Johnson & Johnson)	No PMH No PMH No PMH No PMH	1 day after first dose 14 days after second dose 14 days after the vaccine 10 days after the vaccine	noted on the anterior neck Chest pain Dyspnea Weight loss Dyspnea Weight loss Palpitation Both leg weakness	Not mentioned Not mentioned Not mentioned Not mentioned
[34]	40/F 28/F	Pfizer/ BioNTech Pfizer/ BioNTech	Covid-19 HTN Infertility No PMH	2 days after the vaccine 3 days after the vaccine	neck swelling Nausea, vomiting, fatigue, insomnia, palpitations, fine distal tremors, increased stretch reflexes, and arhythmic heart sounds Anxiety, insomnia, palpitations, and a distal tremor	Propranolol Diltiazem Ivabradine Thiamazole Propranolol Thiamazole	Our case	42/M	Sputnik V (Gam-COVID- Vac)	Covid-19 6 months ago	7 days after first dose	Neck pain, swelling, difficulty in swallowing, occasional hot flashes, palpation, tremor, fatigue, and malaise	Naproxen Prednisolone
[35]	39/F 73/F	AstraZeneca AstraZeneca	No PMH	4 days after second dose 11 days after first dose	Neck pain Fever Neck pain Fever	Not mentioned							
	39/ M	Janssen (Johnson & Johnson)	No PMH	14 days after the vaccine	Neck pain	Not mentioned							

S study, F female, M male, PMH past medical history, HTN hypertension, NSAID nonsteroidal anti-inflammatory drug, SAT subacute thyroiditis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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