

Adenopathy and subacute thyroiditis following CanSino anti-SARS-CoV-2 vaccine

Monika Palacios Martínez,¹ Rafael Bojalil Parra²

Adenopatía y tiroiditis subaguda posterior a la vacunación contra SARS-CoV-2 con CanSino

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Abstract

En the last years, the world has gone through a not very encouraging panorama with the appearance of the SARS-CoV-2 pandemic. The development of vaccines with different technologies has allowed a better control of COVID-19. Vaccines are not exempt from adverse events at the time or after their application. We present the case of a 43-year-old Latina woman who after 12 days application of the recombinant novel coronavirus vaccine (adenovirus type 5 vector) CanSino, CanSino Biologics Inc. ("CanSino BIO") (SSE: 688185, HKEX: 06185) developed axillary and infraclavicular adenopathy; she also developed subacute thyroiditis 4 months later. Both pathologies are related to viral processes and the immunologic response to them. To date there are no reports of the appearance of both conditions in the same patient and there is no information of these adverse events with the application of the CanSino vaccine.

PALABRAS CLAVE

lymphadenopathy; vaccine; subacute thyroiditis; SARS-CoV-2

Resumen

En los últimos años, el mundo ha atravesado un panorama poco alentador con la aparición de la pandemia de SARS-CoV-2. El desarrollo de vacunas con diferentes tecnologías ha permitido un mejor control del COVID-19. Las vacunas no están exentas de eventos adversos en el momento o después de su aplicación. Presentamos el caso de una mujer latina de 43 años que tras 12 días de aplicación de la nueva vacuna recombinante contra coronavirus (vector adenovirus tipo 5) CanSino, CanSino Biologics Inc. («CanSino BIO») (SSE: 688185, HKEX: 06185) desarrolló adenopatía axilar e infraclavicular; también desarrolló tiroiditis subaguda 4 meses después. Ambas patologías están relacionadas con procesos víricos y la respuesta inmunológica a los mismos. Hasta la fecha no existen reportes de la aparición de ambas afecciones en la misma paciente y no hay información de estos eventos adversos con la aplicación de la vacuna CanSino.

KEY WORDS

linfadenopatía; vacuna; tiroiditis subaguda; SARS-CoV-2

¹ Universidad Autónoma Metropolitana, México. ORCID: 0000-0001-6777-9918. Correo de contacto: mpalacios@correo.xoc.uam.mx ² Universidad Autónoma Metropolitana, México. ORCID: 0000-0002-5806-3675.

Introduction

SARS-CoV-2, a virus of the family of *Betacoronaviridae*, is the etiological agent of COVID-19 disease, a severe illness with the first official case described in December 2019, China.¹ According to the World Health Organization (WHO) statistics, as of March 27, 2021, more than 125 million people worldwide have been infected, and more than 2.700.000 have died.²

Several technologies are currently available for the manufacture of vaccines for the prevention of SARS-CoV-2. These include the use of viral vectors (adenoviruses), mRNA in lipid micelles, attenuated viruses, or recombinant proteins. However, to date, there are several articles that talk about the technology used for the development of various vaccines such as Pfizer, Moderna, AstraZeneca, among others, but there is no specific information about the CanSino vaccine or about its side effects in individuals, after its application.³

In the case of anti-coronavirus vaccines, particularly with mRNA vaccines (Pfizer-BioNTech and Moderna), the development of lymphadenopathies has been observed, basically unilateral axillary and/or supraclavicular, mainly in women.⁴ But the adenopathy is not infrequently reported among the adverse effects of different vaccines because it is confused with other pathologies such as cancer. Lymphadenopathy, defined as an abnormality in the size or consistency of lymph nodes can be typically explained by an identifiable regional injury or infection.³ Like many vaccines, mRNA vaccines depend on antigen-presenting cells migrating to regional lymph nodes to elicit both a cellular (T-cell) and humoral (B-cell) immune response stimulating CD4+ and CD8+ T cells responses and high neutralizing antibody titers. Compared with protein-based vaccines, mRNA vaccines elicit a more robust and rapid B-cell proliferation in the germinal center of the lymph.⁵

On the other hand, cases of subacute thyroiditis, Subacute thyroiditis (SAT) is not a pure inflammatory disease but an inflammatory reaction to viral infection, have also been reported in women with certain types of SARS-CoV-2 vaccines inoculation from China, German Northamerican and Sweden, like CoronaVac, Comirnaty, Pfizer, Vaxzevria and Spikevax, respectively.^{6,7} It is known that one of the causes of acute thyroiditis is the presence of viral pathogens, but not the application of biological products such as vaccines. However, the influenza vaccine can cause this pathology and, as has been seen lately, also the one applied against SARS-CoV-2.⁸

Here we present a case where both adverse events associated with vaccination with recombinant coronavirus vaccine, adenovirus type 5 vector, CanSino (CanSino Biologics Inc., China, SSE: 688185, HKEX: 06185) developed: a subacute thyroiditis 4 months post-vaccination, preceded by the presence of axillary and infraclavicular adenopathy, detected 2 weeks post-vaccination. To the best of our knowledge, to date there is no report like this case associated with the CanSino vaccine. As far as we know, to date there is no such report associated with the CanSino vaccine, as mentioned above, or of patients with adenopathy, or of patients with subacute thyroiditis, or both.

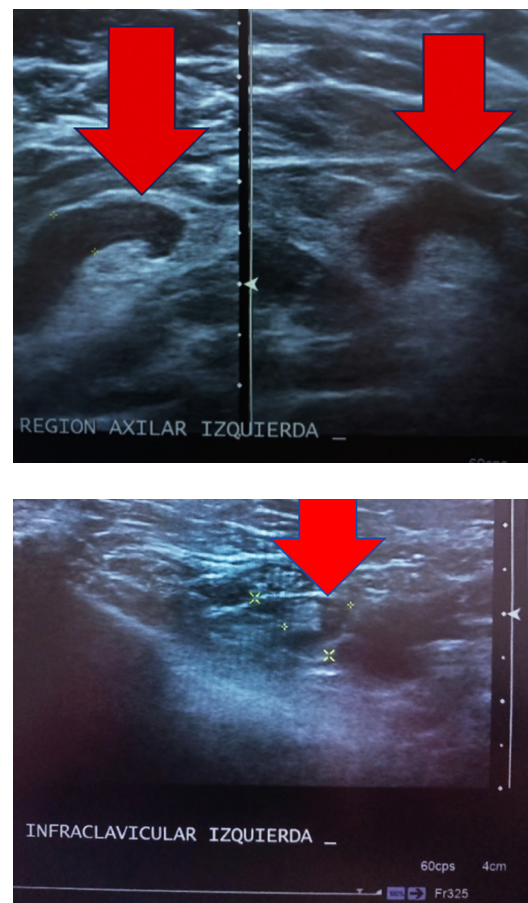
Development

A 43-year-old female patient with a history of right hemithyroidectomy for benign nodule 2 cm in diameter in February 2011, with normal thyroid function, otherwise healthy. She received the CanSino vaccine in the left deltoid muscle on May 22, 2021. The first days of June the patient started with left axillary pain and went to the radiology service to perform an ultrasound (June 3) showed left axillary and ipsilateral infraclavicular nodes with inflammatory appearance (Figures 1 and 2), with mammary images within normal limits.

She was managed with nonsteroidal anti-inflammatory drugs

Figure 1 and 2

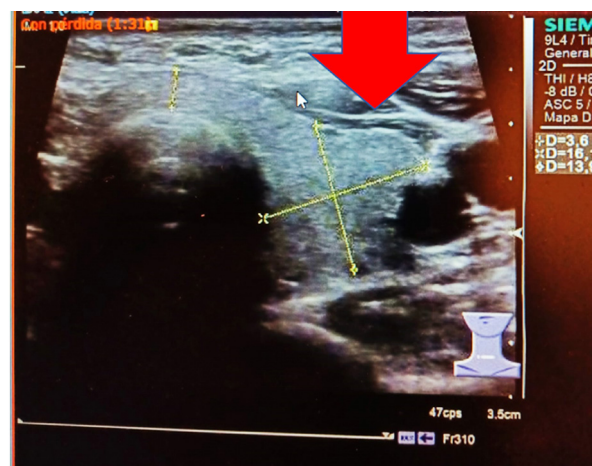
A 43-year-old woman with palpable unilateral axillary adenopathy after receiving the unique dose of the CanSino COVID-19 vaccine in his left deltoid muscle.



Source: own elaboration.

Figure 3

A 43-year-old woman with thyroiditis after receiving the unique dose of the CanSino COVID-19 vaccine in his left deltoid muscle



Source: own elaboration.

(NSAID) for three weeks. The discomfort continued, so almost 3 months after vaccination (August 13) other blood studies were performed including Monotest. Anti- SARS-CoV-2 S-protein antibodies (electrochemiluminescence), leukocyte populations and lymphocyte subpopulations were also measured. All values were within their normal ranges, except for B lymphocytes which are well below normal values for adults, suggesting that the most likely cause of the adenopathy was vaccination because she had never shown any lymphadenopathy or breast problem (Table 1).

Subsequently, 4 months post vaccination, the patient began to refer pain in the left lobe of the thyroid, which prevented her from speaking and swallowing, so an ultrasonographic study was performed (September 30) which showed no alterations of the remaining left lobe (Figure 3). The final diagnosis done by an endocrinologist was subacute thyroiditis secondary to vaccination. She was treated with an NSAID (diclofenac sodium) 50 mg bid for 18 days. Currently the patient is asymptomatic.

In the last years, the world has gone through a health crisis due to SARS-CoV-2, so it was of vital importance to produce vaccines that would help curb the high morbidity and mortality rates presented in the pandemic. The technology that has been used in vaccines has been diverse and its usefulness has been immeasurable. Several studies were conducted to assess the efficacy/effectiveness and safety of the COVID-19 vaccines.⁹ However, there are adverse effects that should be known. Most are mild and transient, ranging from headache, fever, and arm pain at the site of application, to gastrointestinal or hormonal problems.¹⁰ Nonetheless, here are events that can last for weeks or months.

Several vaccines cause adenopathy (smallpox, anthrax, influenza, human papillomavirus) probably due to the induced immune response; those developed against SARS-CoV-2 are not spared. Most of the reported cases of these vaccines have followed two doses with Pfizer or Moderna (Biotech, Spain) biologics or one dose of AstraZeneca (AstraZeneca, Sweden). In several patients, who have received different vaccines (Pfizer and Moderna), adenopathy has appeared 2-4 days after vaccination, however its duration may vary between the two vaccines, being with Pfizer of up to 10 days and with modern of only 2 days. It should also be considered that this variation cannot be caused by the vaccine, but by the intensity of the immune response of everyone. It must be considered that the production of inflammatory interleukins plays a very important role in the response against SARS-CoV-2.¹¹ However, no one has reported adenopathy caused by CanSino to date. The lymphadenopathy spontaneous resolution varied among a maximum duration of 10 days, until up to 32 days.³ As is in this case, the woman had discomfort for three months, mainly in the infraclavicular nodes.

Many of the cases of lymphadenopathy are reported in women, probably due to the relationship they have with hormones, mainly estrogens, although there are also cases of men with this pathology. Therefore, more studies are needed to clarify this behavior.³

Many times, this adverse event has been associated with malignant pathologies in patients who have had a history of breast cancer.¹² Becoming another characteristic of cancer patient, secondary to vaccination against COVID-19.¹³ In patients with current or past history of malignancy, vaccine-related adenopathy can be indistinguishable from nodal metastasis. Therefore, the patient's COVID-19 vaccination history should always be incorporating the patient's COVID-19 vaccination history, including vaccination date and laterality, is critical to optimizing assessment and management of imaging-detected axillary adenopathy in women with otherwise normal breast imaging findings.¹⁴

Radiologists, oncologists, and internists should be aware of this phenomenon, and the booster dose history should be meticulously evaluated in each patient before image interpretation with the knowledge that it may occur quickly as it was present in 1-2 days post-vaccination.¹³ The most presented lymphadenopathies are cervical and axillary, on the side where the vaccine was applied. Although there are studies where you point out atypical places of the presentation of adenopathy. It has founded atypical location in 5/64 patients (7.8 %), including lymphadenopathy in the infraclavicular station (3.1 %), one in the pectoralis major muscle (1.6 %), one in the left arm (1.6 %), and one in the nuchal site (1.6 %). However, reports lymphadenopathy axillary 82.3 % (65/79), supraclavicular 11.4 %

Table 1

A 43-year-old woman results of laboratory studies

Exam	Value
Leukocytes	4.6 10 ⁹ /μL
Erythrocytes	4.69 10 ⁶ /μL
Hemoglobin	13.5 g/dL
Hematocrit	41.3 %
Mean corpuscular hemoglobin	28.8 pg
Platelets	12.8 10 ⁹ /μL
Neutrophils	64.4 %
Lymphocytes	24.5 %
Monocytes	8.2 %
Eosinophils	2.6 %
Basophils	0.3 %
Glucose	83 mg/dL
Urea Nitrogen	15.5 mg/dL
Creatinine	0.8 mg/dL
Urea nitrogen/creatinine ratio	19.4
Uric acid	3.7 mg/dL
Calcium	9 mg/dL
Phosphorus	3.7 mg/dL
Sodium	142 mEq/L
Potassium	4.2 mEq/L
Chlorine	111 mEq/L
Total cholesterol	182 mg/dL
High density lipoprotein (HDL) cholesterol	38.1 mg/dL
Low-density lipoprotein (LDL) cholesterol	120.5 mg/dL
Very low density lipoprotein cholesterol (VLDL)	23.4 mg/dL
Triglycerides	117 mg/dL
Total protein	6.7 g/dL
Albumin	4.1 g/dL
Globulins	2.6 g/dL
Total bilirubin	0.5 mg/dL
Aspartate aminotransferase (GOT)	22 UI/L
Alanine aminotransferase (GPT)	26 UI/L
Alkaline phosphatase	43 UI/L
Gamma glutamyl transpeptidase (GGT)	10 UI/L
Lactate dehydrogenase	135 UI/L
HETEROPHILIC AC MONOTEST	Negativo
SARS-COV-2 TOTAL ANTI-S ACS	436.1 U/mL (Threshold 0.8 U/mL)
IT	51.6 %
LB	2.8 %
NK	37.4 %
CD3+	53.6 %
CD3+CD4+	57.9 %
CD3+CD8+	23.3%
CD3+CD4+CD45RA+CD45RO-	21.6 %
CD3+CD4+CD45RA+CD45RO+	14.0 %
CD3+CD4+CD45RA-CD45RO+	64.4 %
CD3+CD8+CD45RA+CD45RO-	30.5 %
CD3+CD8+CD45RA+CD45RO+	26.7 %
CD3+CD8+CD45RA-CD45RO+	42.9 %
CD3+CD4+CD62+	39.9 %
CD3+CD4+CD62-	29.7 %
CD3+CD8+CD28+	50.4 %
CD3+CD8+CD28-	16.3 %

(9/79), infraclavicular 1.2 % (1/79), and subpectoral or neck regions 5.1 %.¹⁵

To date, there are no reports of the occurrence of adenopathy or thyroiditis secondary to CanSino vaccine application. Here we report the subsequent appearance of axillary and infraclavicular adenopathy ipsilateral to the vaccinated arm, with breast ultrasound without pathology data. This case coincides with others reported. For example, an elder female patient without a significant medical history had Pfizer-BioNTech mRNA COVID-19 vaccination 3 days before the examination demonstrated mildly enlarged left axillary and subpectoral lymph nodes.¹⁶ Exist several cases of women who presented adenopathy after the start of vaccination against Covid. Among the serious illnesses that can present with lymphadenopathy, perhaps the most concerning to the patient and physician alike is the possibility of underlying malignancy and.¹⁷

In general practice, less than 1 % of lymphadenopathies are malignant, with that number being 0.4 % in patients under 40 years of age. In one study reveals two pediatric cases of supraclavicular lymphadenopathy following COVID-19 vaccinations. These cases highlight the need to develop assessment guidelines to help prevent potentially harmful diagnostic procedures in the pediatric population.¹⁸

The appearance of post-vaccination adenopathy should not be surprising since an inflammatory response is induced at the injection site, and it is well known that antigens, within dendritic cells, travel to nearby lymph nodes where the adaptive immune response is initiated.¹⁹

In the early appearance of side effects due to the application of vaccines, specifically lymphadenopathies, it is recommended as a first management to rule out whether it is of benign and transient or malignant origin. This is done through imaging techniques or biopsies.¹⁷

Prior to this, the population must be informed about the possible effects of the vaccines, so that now of the presentation of some unwanted effect, the individual takes it calmly and goes to the medical service for its review. And finally, clinical follow-up should be given to those individuals whose adenopathy does not resolve, because it is probably associated with malignant neoplasms such as breast or head/neck cancer, lymphoma, or melanoma.¹²

On the other hand, to date, billions of anti-SARS-CoV-2 vaccines have been used worldwide and reported cases of subacute thyroiditis are less than ten. It is therefore an extremely rare adverse event. The causes of this phenomenon are not yet known, as cases have occurred with vaccines using different technologies. It has been suggested that HLA molecules may be associated with susceptibility.^{6,19,20} One of the causes of subacute thyroiditis is contact with viral agents such as adenovirus, enterovirus, or influenza, among others; currently the presence of subacute thyroiditis has been described with the application of several vaccines against the new coronavirus (Pfizer, Astrazeneca, (Astrazeneca, Sweden), CoronaVac (Sinovac Life Science, China) and Moderna (Biotech, Spain).^{7,21} There are several cases of subacute thyroiditis in people between 35 and 45 years old after vaccination against SARS-CoV-2, who also presented pain in the neck and although this is more commonly caused by mRNA vaccines and other cases that have occurred in women without a thyroid history in the United States and Europe.⁸

To date there is no information on the causes of subacute thyroiditis caused by vaccination, but it is possible to relate the appearance of thyroiditis with the reactivity of viral antigens in mRNA vaccines and with vaccines that use viral vectors like CanSino that uses an adenovirus as a vector. In a study with patients infected with SARS-CoV-2 high levels of IL-6 are present, which may be associated with a systemic storm of cytokines that are damaging the thyroid.⁸

It should be considered that the case reported here has a history of having suffered from a benign thyroid ten years ago, but the patient had never suffered from pain in the neck area, until after the application of the CanSino vaccine. It is important to point out that in this case, she underwent of right hemithyroidectomy 10 years earlier. The case that we report it is also an effect secondary to vaccines with adenovirus viral vector such as the CanSino vaccine. Therefore, inflammation in the thyroid is related to vaccination, since one of the causes of subacute thyroiditis is contact with a virus.

In this case, the treatment was with NSAIDs, as is usually prescribed, although

the other option is glucocorticoids. However, these can interfere with the production of specific antibodies against the virus. In addition to the appearance of other side effects due to its use, it is precisely necessary to evaluate the degree of inflammation and how it affects or puts the patient's health at risk.

Conclusions

Vaccines have historically saved millions of lives. Specifically, those developed to control the new coronavirus have strikingly modified mortality curves. Like virtually all drugs and biologics, vaccines can induce adverse events, and their early identification can help to ameliorate the proper management of patient's signs and symptoms. Our data allow us to suggest that long-term adenopathy and subacute thyroiditis may occur in the same patient after the application of a viral vector (adenovirus) vaccine against SARS-CoV-2 either at the same time or with months of appearance between them, since they are not mutually exclusive. However, more studies are needed for understand the CanSino vaccines and their secondary effects or cases with adverse effects are reported, to compare whether there is a variation between the other vaccines that currently exist. Its known, more studies are needed to understand the CanSino vaccines and their side effects. In addition to how is the immune response produced by said vaccine and thus be able to understand the origin of both pathologies to compare if there is a variation between the other vaccines that currently exist and this vaccine. It is worth mentioning that the patient had Pharmacovigilance follow-up for a period of 5 months after immunization and that there are no similar reports on this vaccine worldwide.

Ethical considerations

The patient agreed to have her case reported and her clinical trial information disseminated for this manuscript.

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conflict of interest

Authors contribution: All authors contributed to the writing and review of the article.

There is no conflict of interest

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