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# Hypersensitivity reaction to hyaluronic acid dermal filler after COVID-19 vaccination: A series of cases in São Paulo, Brazil

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## ABSTRACT

Brazil ranked second in the world for the number of aesthetic procedures carried out in 2019. Five case reports of delayed hypersensitivity reaction to hyaluronic acid dermal filler after COVID-19 vaccination are presented in this paper. Additional vaccination for new variants, including omicron, will be necessary; therefore, aesthetic professionals should be aware of this possibility and advise patients accordingly.

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## Introduction

Brazil ranks third for the number of patients infected with SARS-CoV-2 coronavirus and second for the mortality rate worldwide; however, vaccination is changing the scenario quickly. In São Paulo, by December 15, 2021, 78.0% of the population was fully vaccinated (Vacinômetro Governo do Estado de São Paulo). In 2019, according to the International Society for Aesthetic Surgery (ISAPS), Brazil ranked second for the number of aesthetic procedures performed (Global Survey 2019). Dermal fillers using hyaluronic acid (HA) have become popular for enhancing facial features in recent years (Batista, 2017). It has been reported that after the COVID-19 vaccination, patients may present a delayed hypersensitivity reaction (DHR) in the area where HA was previously applied (Munavalli et al. (a), 2021; Savva et al., 2021)). We report five cases of DHR to HA dermal filler after Pfizer or AstraZeneca COVID-19 vaccination.

## Case 1

A healthy woman aged 35 years had a medical history of use of HA fillers. About 7.0/8.0 mL of HA (Restylane Classic and Restylane Lyft, Galderma) was applied to her lips, nasojugal furrow, malar, and chin regions at three different times. The first application was performed in 2016 in these four indicated areas, and the last application occurred in April 2020 only in the lips and nasojugal furrow regions. A persistent intermittent delayed swelling occurred and she was followed up by her dermatologist. On August 6, 2021, she received her first AstraZeneca COVID-19 vaccine. Twenty-four hours later, she presented with induration and edema in her lips and chin, where HA was previously applied, and was diagnosed with DHR to HA dermal filler after vaccination. She was prescribed with prednisone 20 mg twice a day for 7 days.

After 2 days of steroid use, the edema in the lips and chin region improved, but they appeared in other regions of HA application, which were malar region and nasojugal sulcus. For this reason, prednisone was maintained for a further 7 days, with progressive reduction, completing a total of 21 days of steroid treatment. Although an improvement was achieved, she still remained with mild lip edema. Cushing syndrome developed and the corticosteroid was replaced by hydroxyzine (50 mg/day). On December 15, 2021, mild edema remained on her lips even with the use

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**Figure 1.** Phone camera “selfie” images showing hypersensitivity reactions to HA dermal filler after COVID-19 vaccination. (A) Case 1: induration and edema in the inferior/superior lips (A1 and A2), which remained for 4 months after vaccination (A3). (B) Case 2: edema in the lower eyelids. (C) Case 3: mild edema on the lips. (D1) Case 4: edema in the mandible and chin and a herpes simplex infection in the lips (D2). (E) Case 5: edema and erythema on the lips and chin (E). The patients live in different cities in São Paulo state, Brazil.

of antihistamines; although antihistamines have limited action on DHR (Munavalli et al., 2021a) (Figure 1, A1, A2, and A3).

#### Case 2

In February 2021, 1.0 mL of HA was applied around the eye of a healthy woman aged 47 years. She received the first dose of COVID-19 BNT162b2 (Pfizer-BioNTech) mRNA vaccine in May 2021 and the second dose in August 2021. Four weeks after the second dose she developed DHR with edema in the lower eyelids where HA was applied. She self-medicated with prednisolone 20 mg/day for 4 days with remission after 1 week. In October 2021, she presented with a new episode of DHR and was treated in the same manner. In December 2021, a further episode occurred and treatment with lisinopril 5 mg resulted in an adequate response within 24 hours. The episodes were accompanied by nasal congestion and sneezing (Figure 1B).

#### Case 3

In December 2020, 1.0 mL of HA (Restylane Kisse, Galderma) was applied to the superior and inferior lips of a healthy woman aged 34 years. In October 2021, 24 hours after receiving the third dose of COVID-19 Pfizer-BioNTech vaccine, she presented with DHR to HA dermal filler characterized by pain and mild edema in the lips where HA was applied. She was prescribed loratadine 10 mg per day for 2 days achieving complete resolution in 72 hours and no relapse (Figure 1C).

#### Case 4

In September 2021, 2.0 mL of HA (Restylane lift, Galderma) was applied to the mandibula (jaw angle) and chin and 1.0 mL (Vital Light, Galderma) to the lips of a healthy women aged 56 years. Forty-eight hours after receiving the COVID-19 Pfizer-BioNTech vaccine, she presented with DHR characterized by induration and edema in the mandible and chin where HA was applied. She was treated with oral prednisone 20 mg twice a day for 3 days and complete resolution was achieved (Figure 1, D1). She developed herpes simplex virus lesions in her lips immediately after vaccination. She was treated with valaciclovir 500 mg twice a day for 5

days and oral prednisone 20 mg twice a day for 3 days achieving complete resolution (Figure 1, D2).

#### Case 5

In May 2020, 2.0 ml of HA (Revanesse® Versa) was applied to the nasolabial folds and lips of a healthy woman aged 43 years without any complications. In May 2021, the procedure was repeated only on her lips with 1.0 mL of HA (Revanesse® Versa). Fifteen days later, she received the second dose of the COVID-19 AstraZeneca vaccine. One week later she presented with edema, erythema, increase in the temperature of her lips, fever, sensation of fatigue, and purpuric lesions of the extremities. She was treated with ibuprofen 40 mg/day and prednisone 40 mg/day, and her symptoms reduced after 1 week. Prednisone was progressively decreased and stopped after 3 weeks (Figure 1E).

#### Discussion

All these case reports showed a hypersensitivity reaction to HA dermal filler more than 24 hours after vaccination for COVID-19, characterized by a delayed or type IV hypersensitivity reaction, a cell-mediated hypersensitivity triggered by T lymphocytes (Turkmani et al., 2019; Munavalli et al., 2021a; Rowland-Warmann 2021; Savva et al., 2021)). However, several published reports suggested that causes other than COVID-19 vaccines may be involved in the etiology of DHR to HA dermal filler such as viral infections and trauma, filler volume, repeat treatments, intramuscular implantation, and different properties of HA fillers (Turkmani et al., 2019).

In 2020, 21.0% of the entire population of Brazil lived in São Paulo state, estimated to be 213,930,425 inhabitants according to the Brazilian Census (Instituto Brasileiro de Geografia e Estatística (IBGE) 2021). Since 1973, the vaccine culture in Brazil has been stringent and at the end of 2021, Brazil was one of the most vaccinated countries for COVID-19. More than 51% of the population of the country comprises women and 57.7% are more than 30 years of age and are potential clients for aesthetic procedure. It is noteworthy that in recent times there is an increasing demand in men for aesthetic procedures too. In 2019, HA was applied in 398,830 procedures in the country (Global Survey, 2019).

It is still not known which individuals progress to DHR after COVID-19 vaccination, how long the application of HA is most likely to produce a reaction, and the wait time after COVID-19 vaccine for HA dermal filler. Treatment with HA in our case reports varied from weeks to months before vaccination, and although most reactions resolved after a few days, some are recalcitrant with periods of improvement, worsening, and recurrence months after the application of the vaccine. In most cases, treatment involves antihistamines, oral corticoids, and application of hyaluronidase or lisinopril (Munavalli et al., 2021a,b). Corticosteroids down-regulates the immune response to vaccines and produce an array of side effects. In our case reports, individual in case 1 evolved with Cushing syndrome and individual in case 4 evolved with herpes simplex virus infection after treatment with prednisone. However, the individual in case 2 was treated with lisinopril, a new therapeutic tool to treat DHR to dermal HA fillers after COVID-19 vaccination. Lisinopril is an oral angiotensin-converting enzyme inhibitor (ACE-I), which decreases the cutaneous HA filler-related inflammatory reaction and edema in patients vaccinated to COVID-19. ACE-I has also been previously reported to have therapeutic value in the treatment of other cutaneous disorders, and different mechanisms are proposed to explain the anti-inflammatory properties of ACE-I. Furthermore, it was suggested that lisinopril can be used not only to treat DHR but also to minimize the risk of DHR after the second dose of the COVID-19 vaccine if the reaction had occurred previously (Munavalli et al., 2021a,b).

Waves of new variants are now appearing; the omicron variant carries about 50 mutations not seen in combination before (World Health Organization 2021). Extra protection against the virus will likely require new vaccine formulations, raising questions on whether booster doses will need to be continued indefinitely, increasing the possibility of DHR in patients previously treated with HA. We suggest that, countrywide, a large number of women vaccinated for COVID-19, who had previously had HA applied, experienced DHR, which has gone unreported.

In Brazil, adverse event following immunization (AEFI) of COVID-19 surveillance actions are aimed at moderate and severe events and must be immediately notified in an online available file “Post-vaccination adverse event notification/investigation form” to the Ministry of Health Surveillance Department, Communicable Disease Surveillance Department, General Coordination of the National Immunization Program. The case will be addressed to the Epidemiological Surveillance Center (GVE) of São Paulo state, investigated and clarified so that the immunization program and the epidemiological safety of the entire population is not jeopardized. It is noteworthy that from the five cases reported in this paper, only one patient was notified to GVE.

As vaccination for COVID-19 rolls out to members of all eligible adult demographics, DHR to dermal fillers could become the most common one among AEFIs; therefore, doctors should obtain informed consent from the patients regarding the hypersensitivity reaction that might take place after HA fillers and COVID-19 vaccination.

We conclude that, mainly in Brazil, our report is important for aesthetic professionals to be aware of this event, notify health care authorities of this possible reaction, and advise patients of this possibility.

## Contributions

Luciana Cegatto Martins Ortigosa: Writing, provided patients to the study

Fabiano Lenzoni: provided patients to the study

Maria Victória Suárez: provided patients to the study

Artur Antônio Duarte: provided patients to the study

Luiz Euribel Prestes-Carneiro: Study design, data collection, and writing

## Conflict of Interest

The authors declare no financial or other competing interests associated with this publication.

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## Ethical approval statement

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