



Treatment of delayed inflammatory response to hyaluronic acid soft tissue filler in a Pfizer-Boosted Moderna-Vaccinated individual with hyaluronidase

Tratamento da resposta inflamatória tardia ao preenchimento de tecidual com ácido hialurônico em indivíduo imunizado Moderna após reforço com vacina Pfizer com hialuronidase

DOI: <http://www.dx.doi.org/10.5935/scd1984-8773.2022140149>

ABSTRACT

We present a case of delayed-type hypersensitivity to hyaluronic acid (HA)-based filler on the face following the Pfizer booster in a Moderna-vaccinated individual. It is the first known case of treatment of the delayed-type hypersensitivity reaction with hyaluronidase following Covid vaccination. Hyaluronidase is a viable option to treat this reaction, particularly for patients who may not benefit from systemic treatment options. With an anticipated fourth round of vaccine boosters on the horizon, there may be an increased incidence of cutaneous adverse events, including the reaction discussed.

Keywords: COVID-19; SARS-CoV-2; Inflammation; Dermal fillers; Hypersensitivity; Delayed; Hyaluronic acid

RESUMO

Apresentamos um caso de hipersensibilidade tardia ao preenchimento à base de ácido hialurônico na face após o reforço da vacina Pfizer em um indivíduo imunizado com Moderna. Este é o primeiro caso conhecido de tratamento da reação de hipersensibilidade tardia com hialuronidase após a vacinação anti-Covid. A hialuronidase é uma opção viável para tratar esta reação, particularmente para pacientes que podem não se favorecer com as opções de tratamento sistêmico. Com uma quarta ronda de reforço de vacinas planejada no horizonte, pode haver um aumento da incidência de eventos adversos cutâneos, incluindo a reação discutida.

Palavras-chave: COVID-19; SARS-CoV-2; Inflamação; Preenchedores dérmicos; Hipersensibilidade tardia; Ácido hialurônico

Case Report

Authors:

Sabine Obagi¹
Zaidal Obagi²
Yasmeen Altawaty³
Zein Obagi⁴

- ¹ University of Arizona College of Medicine, Tucson (AZ), United States
- ² University of Arizona College of Medicine, Division of Dermatology, Tucson (AZ), United States
- ³ Western University of Health Sciences, College of Pharmacy, Pomona (CA), United States
- ⁴ ZO Skin Health Institute, Beverly Hills (CA), United States

Correspondence:

Sabine Obagi
Email: sobagi@bu.edu

Financial support: None
Conflict of interest: None

Submitted on: 11/05/2022
Approved on: 13/06/2022

How to cite this article:

Obagi S, Obagi Z, Altawaty Y, Obagi Z. Treatment of delayed inflammatory response to hyaluronic acid soft tissue filler in a Pfizer-Boosted Moderna-Vaccinated individual with hyaluronidase. Surg Cosmet Dermatol. 2022;14:e20220149.



INTRODUCTION

The Covid-19 pandemic has presented numerous challenges that the literature continues to explore. Throughout the pandemic, aesthetic procedures persisted, with aesthetic plastic surgery generating a total revenue of over \$9 billion in 2020.¹ With the advent of the Covid vaccines, literature regarding the safety, efficacy, and adverse events have become of great interest to clinicians and the public.

Dermal fillers, neurotoxin injections, peels, and subcutaneous augmentations represent an ever-growing portion of cosmetic and surgical dermatology, and a 36–58% annual increase in dermal fillers was observed over the past few years. In 2020, about 1.3 million of these procedures were performed.²

Another round of boosters is underway, and the US Food and Drug Administration (FDA) recently approved the fourth Covid shot. The rise in filler popularity represents a significant population at risk for developing adverse reactions due to Covid vaccinations.

To date, five case reports have been published regarding delayed hypersensitivity reactions to soft-tissue fillers following Moderna and Pfizer vaccination, all on hyaluronic acid (HA)-based fillers. Steroids, antihistamines, and ACE inhibitors have been documented as possible treatments for this reaction.³⁻⁷

We present a case of delayed hypersensitivity to HA-based filler on the face following the Pfizer booster in a Moderna-vaccinated individual. Oral inflammation was self-resolved, but persistent inflammation of the infraorbital and trochlear region only resolved after hyaluronidase administration. Hyaluronidase (HAse) injection is used off-label for dissolving HA-based fillers.⁸ It is the first known case of treatment of the delayed hypersensitivity reaction to HA following Covid vaccination with hyaluronidase. Also, it is another option to treat this reaction, particularly for patients who may not benefit from systemic therapy.

CASE PRESENTATION

A 29-year-old woman with a history of dermal fillers and no known medical conditions or allergies presented to the clinic with swelling of the bilateral vermillion (Figure 1A) and the bilateral under-eye compartments (Figure 2A), occurring 36–48 hours post-Pfizer booster. The patient reported a milder reaction after her second Moderna vaccination in the same areas, which self-resolved. She denied any tongue swelling or trouble breathing.

Four months before this reaction, the patient received HA dermal fillers: Juvederm Ultra XC 0.2 mL to the top lip and 0.1 mL to the bottom lip. She also received 0.5 mL of Belotero injected into each under-eye region.

The patient denied any history of infection, trauma, rosacea, or granulomatous cheilitis and did not have any new fillers injected since receiving her first two Covid vaccinations. The swelling only occurred at the filler sites: no additional swelling was noted elsewhere.



Figure 1: **A** - 36-48 hours following the Pfizer booster. Note the enlarged and edematous upper and lower lips, which may be mistaken for angioedema. **B** - Lips two weeks following conservative management.

The patient was diagnosed with delayed hypersensitivity to the dermal fillers following Covid vaccination. She opted for monitoring and non-medical treatments. The patient applied ice intermittently to the affected areas at home. After 48–72 hours, her lip swelling had resolved, but the inflammation around her eyes persisted.

After four days, the patient continued to have persistent swelling around the eyes and returned to the clinic. Each infraorbital area that contained the previous filler received 50 units of hyaluronidase mixed with saline.

By the following day, the patient reported complete resolution of the swelling of the bilateral periorbital region and total satisfaction with the treatment. She had no further complications at her follow-up appointment two weeks later (Figures 1B and 2B).

DISCUSSION

The 2019 American Society of Plastic Surgeons Statistics Report showed that soft-tissue fillers represent the second most common minimally invasive cosmetic procedure following Botox. HA-based dermal fillers made up 79% of the 2.7 million fillers in 2019.⁹ HA-based dermal fillers can last between 6 to



FIGURE 2: **A** - 36-48 hours following the Pfizer booster. Note the inflamed and edematous skin overlying the infraorbital and lacrimal duct region. **B** - The eye of the same patient two weeks following hyaluronidase dissolution of under eye filler.

18 months and are preferred for their safety profile as an injection of hyaluronidase, an enzyme that hydrolyzes the filler, can instantly reverse them.

Although well tolerated, the rise in filler treatments has led to an increase in adverse events reported, including delayed hypersensitivity reactions to HA-filler. To date, five case reports have described this reaction. Various treatments were tried in these cases, such as antihistamines, steroids, and ACE inhibitors, nearly all with eventual resolution. We found no documented case involving hyaluronidase as a mechanism of treatment.³⁻⁷

Hypersensitivity reactions are classified into acute and delayed. Acute hypersensitivity reactions onset within minutes to hours from injection time and are immunoglobulin-E mediated. They can result in an anaphylactic reaction or swelling and often present as urticaria or angioedema.¹⁰ Mild forms of this reaction respond well to antihistamines and topical or oral steroids, while severe cases require systemic treatments.

The mechanism of action of delayed hypersensitivity involves cell-mediated responses with downstream signaling unli-

kely to respond to OTC antihistamines. The mechanism to sensitize dermal fillers following Covid vaccination is unclear but is likely to be multifactorial, involving cross-reactivity and possibly epitope spreading.

Munavalli et al. suggest the potential mechanism of the delayed inflammatory reaction to HA fillers in Covid-19-related cases, involving the binding and blockade of ACE2 receptors, which are targeted by the SARS-CoV-2 virus spike protein to gain entry into the cell.¹¹ Munavalli postulates that cross-reactivity between the spike protein and dermal ACE-2 receptors forms an antigenic response favoring a pro-inflammatory, loco-regional TH1 cascade, then promoting a CD8+T cell-mediated reaction and leading to incipient granulomas formed around residual HA particles. They support this with evidence of clinical response of dermal filler inflammation to oral ACE-inhibitors.¹¹

We present a case using hyaluronidase to improve the delayed inflammatory response following the Pfizer Covid-19 booster. Hyaluronidase injection as an alternative method to improve the inflammatory response can be an amenable option for patients unable or unwilling to take systemic medication.

Pre-existing data support the treatment with hyaluronidase for hypersensitivity reactions to HA-based fillers from other etiologies. DeLorenzi et al. report that soft tissue injection of hyaluronidase alone, without any ancillary treatments, has provided excellent results to hypersensitivity reactions to fillers, superior to his previous protocol.^{12,13}

Clinicians should recognize the benefit of hyaluronidase in certain medical conditions and may collaborate with pharmacists to achieve an appropriate dose and method of administration.

A medical professional must administer hyaluronidase. Also, patients must be adequately hydrated pre-treatment and monitored post-treatment for signs of thrombosis, anaphylaxis, and injection site reactions.¹⁴ Hyaluronidase injections should be avoided in patients with allergies to bovine collagen and bee stings due to potential cross-reactions.⁸

On March 29, 2022, the US FDA authorized a second booster dose of the Pfizer or Moderna vaccine for older and some immunocompromised individuals. With an anticipated fourth round of vaccine boosters on the horizon, there may be an increased incidence of cutaneous adverse events, including the reaction discussed.

Future studies are needed to develop a comprehensive understanding and treatment protocol for Covid-19 vaccine-related HA-based filler complications, considering patients' comorbidities and medication safety. Patients should be wary of more severe reactions with subsequent vaccinations, as seen in our patient, who had a mild response after the second Covid vaccine and a serious reaction after the booster. ●

REFERENCES:

1. Surgery. 2021. The Aesthetic Society Releases Annual Statistics Revealing Americans Spent Over \$9 Billion on Aesthetic Plastic Surgery in 2020. [online] Available at: <https://www.surgery.org/media/news-releases/the-aesthetic-society-stats-reveal-americans-spent-over-9-billion-aesthetic-plastic-surgery-2020>.
2. CDN. 2020. Aesthetic Plastic Surgery National Databank Statistics 2020. [PDF] The Aesthetic Society. Available at: <https://cdn.theaestheticsociety.org/media/statistics/aestheticplasticsurgerynationaldatabank-2020stats.pdf>
3. Michon A. Hyaluronic acid soft tissue filler delayed inflammatory reaction following COVID-19 vaccination - A case report. *J Cosmet Dermatol.* 2021;20(9):2684-90.
4. Savva D, Battineni G, Amenta F, Nittari G. Hypersensitivity reaction to hyaluronic acid dermal filler after the Pfizer vaccination against SARS-CoV-2. *Int J Infect Dis.* 2021;113:233-5.
5. Munavalli GG, Guthridge R, Knutsen-Larson S, Brodsky A, Matthew E, Landau M. "COVID-19/SARS-CoV-2 virus spike protein-related delayed inflammatory reaction to hyaluronic acid dermal fillers: a challenging clinical conundrum in diagnosis and treatment". *Arch Dermatol Res.* 2022;314(1):1-15.
6. Rowland-Warmann MJ. Hypersensitivity reaction to Hyaluronic Acid Dermal filler following novel Coronavirus infection - a case report. *J Cosmet Dermatol.* 2021;20(5):1557-62.
7. Shome D, Doshi K, Vadera S, Kapoor R. Delayed hypersensitivity reaction to hyaluronic acid dermal filler post-COVID-19 viral infection. *J Cosmet Dermatol.* 2021;20(5):1549-50.
8. Jung H. Hyaluronidase: an overview of its properties, applications, and side effects. *Arch Plast Surg.* 2020;47(4):297-300.
9. Plastic Surgery. 2019. National Plastic Surgery Statistics. [PDF] American Society of Plastic Surgeons. Available at: <https://www.plasticsurgery.org/documents/News/Statistics/2019/plastic-surgery-statistics-report-2019.pdf>
10. Arron ST, Neuhaus IM. Persistent delayed-type hypersensitivity reaction to injectable non-animal-stabilized hyaluronic acid. *J Cosmet Dermatol.* 2007;6(3):167-71.
11. Munavalli GG, Knutsen-Larson S, Lupo MP, Geronemus RG. Oral angiotensin-converting enzyme inhibitors for treatment of delayed inflammatory reaction to dermal hyaluronic acid fillers following COVID-19 vaccination-a model for inhibition of angiotensin II-induced cutaneous inflammation. *JAAD Case Rep.* 2021;10:63-8.
12. DeLorenzi C. New high dose pulsed hyaluronidase protocol for hyaluronic acid filler vascular adverse events. *Aesthet Surg J.* 2017;37(7):814-25.
13. Gilson RL, Zafar Gondal A. Hyaluronidase. [Updated 2021 Jun 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.
14. CDC. 2022. Centers for Disease Control and Prevention. Available at: <https://www.cdc.gov/media/releases/2022/s0328-covid-19-boosters.html>.

AUTHORS' CONTRIBUTION:

Sabine Obagi  ORCID_0000-0002-1294-547X

Approval of the final version of the manuscript; study design and planning; preparation and writing of the manuscript; data collection, analysis, and interpretation; active participation in research orientation; intellectual participation in propaedeutic and/or therapeutic conduct of studied cases; critical literature review; critical revision of the manuscript.

Zaidal Obagi  ORCID_0000-0001-5773-8039

Approval of the final version of the manuscript; study design and planning; active participation in research orientation.

Yasmeen Altawaty  ORCID_0000-0002-8189-2375

Data collection, analysis and interpretation.

Zein Obagi  ORCID_0000-0002-3350-8586

Study conception and planning.