



Review Article

Delayed inflammatory reaction to hyaluronic acid filler following COVID-19 vaccination: A case report and review of the literature

Noureddine Litaïem¹, Mariem Fazzeni¹, Abdulmooti Hawilo², Faten Zeglaoui¹

¹Department of Dermatology, Charles Nicolle Hospital, University of Tunis el Manar, Tunis, Tunisia, ²Department of Dermatology, MMC Hospital, Medina, Saudi Arabia.

***Corresponding author:**

Noureddine Litaïem,
Department of Dermatology,
Charles Nicolle Hospital,
University of Tunis el Manar,
Tunis, Tunisia.
noureddine.litaïem@gmail.com

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ABSTRACT

Delayed inflammatory reactions (DIRs) to coronavirus disease 2019 (COVID-19) vaccines were rarely reported in patients receiving hyaluronic acid (HA) soft-tissue fillers. We present a case of a DIR to HA filler that occurred within days after receiving the second dose of the Pfizer-BioNTech COVID-19 messenger ribonucleic acid (RNA) vaccine and provide a comprehensive summary of its clinical presentation and treatment.

Keywords: Hyaluronic acid, Dermal fillers, Injection site reaction, Adverse effects, COVID-19, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Vaccination, Vaccines, Messenger RNA

INTRODUCTION

Hyaluronic acid (HA) is one of the most important ingredients in cosmetic products due to its remarkable anti-aging properties. This can be achieved through soft-tissue augmentation, improved skin hydration, collagen and elastin stimulation, and face volume restoration.¹ The use of HA soft-tissue fillers for non-invasive esthetic procedures is rapidly increasing. In 2022 alone, over 4 million HA soft-tissue filler procedures were performed worldwide, making it the second most performed non-surgical procedure.²

With the emergence of coronavirus disease 2019 (COVID-19) vaccines, practitioners have raised concerns about the safety of HA-based fillers during the pandemic. However, the frequency of complications that could be attributed to COVID-19 disease or vaccination was low (0.06%).³

Delayed inflammatory reactions (DIRs) to fillers are defined as reactions occurring at least 2–4 weeks after injections and could manifest as discoloration (most commonly erythema), painful nodules, localized induration, and edema.⁴

DIRs to COVID-19 vaccines were rarely reported in patients receiving HA soft-tissue fillers.^{5–15} Its pathophysiological mechanism is not fully understood, and its treatment is not well codified. We present a case of a DIR to HA filler that occurred within days after receiving the second dose of the Pfizer-BioNTech COVID-19 messenger ribonucleic acid (RNA) vaccine and provide a comprehensive summary of its clinical presentation and treatment.

CASE REPORT

A 43-year-old female, physically fit and healthy, without any personal or family history of atopy, urticaria, or known drug allergies, presented with intermittent swelling of the lower eyelids for 2 weeks. She denied any prior inflammatory filler reactions. In June 2020, the patient received 3 ml of HA soft-tissue filler, with 1 ml of Juvederm Volbella and 2 mL of Juvederm Ultra, equally injected into her bilateral tear troughs to correct under eye hollowness. The injection was performed in the subdermal plane using a microcannula under proper sterile conditions. In March 2021, 3 days after receiving the second dose of the mRNA Pfizer-BioNTech COVID-19 vaccine, the patient reported moderate swelling and tenderness in her bilateral tear troughs. There was no recent history of trauma or infection, and she had not taken any medications recently. The examination revealed edema of the lower eyelids, mainly on the right side, but without erythema and mild tenderness on touch [Figure 1]. No palpable nodule or fluctuant mass was found. Magnetic resonance imaging showed multiple bilateral tiny foci of high transverse relaxation time (T2) signal rounded material and bilateral cosmetic material injection (filler) seen within maxilla and nasolabial folds with mild contour asymmetry, being larger on the right in the axial fluid-attenuated inversion recovery images [Figure 2]. Based on the appearance of localized edema within days after receiving the mRNA COVID-19 vaccine, the diagnosis of DIR secondary to the vaccine was made, as no other triggers, such as infection, trauma, dental, or medical procedures, were found. The patient received initial treatment with oral prednisone, 40 mg daily, which reduced swelling but resulted in recurrence after treatment tapering. The patient was subsequently started on a daily dose of 5 mg lisinopril, resulting in substantial improvement within 6 h [Figure 1] and complete resolution without recurrence at follow-up.



Figure 1: (a) Edema of the lower eyelids following coronavirus disease 2019 (COVID-19) vaccination. (b) Rapid resolution after lisinopril initiation.

DISCUSSION

All HA dermal fillers carry a risk of both acute and delayed reactions. Acute reactions can manifest as injection site

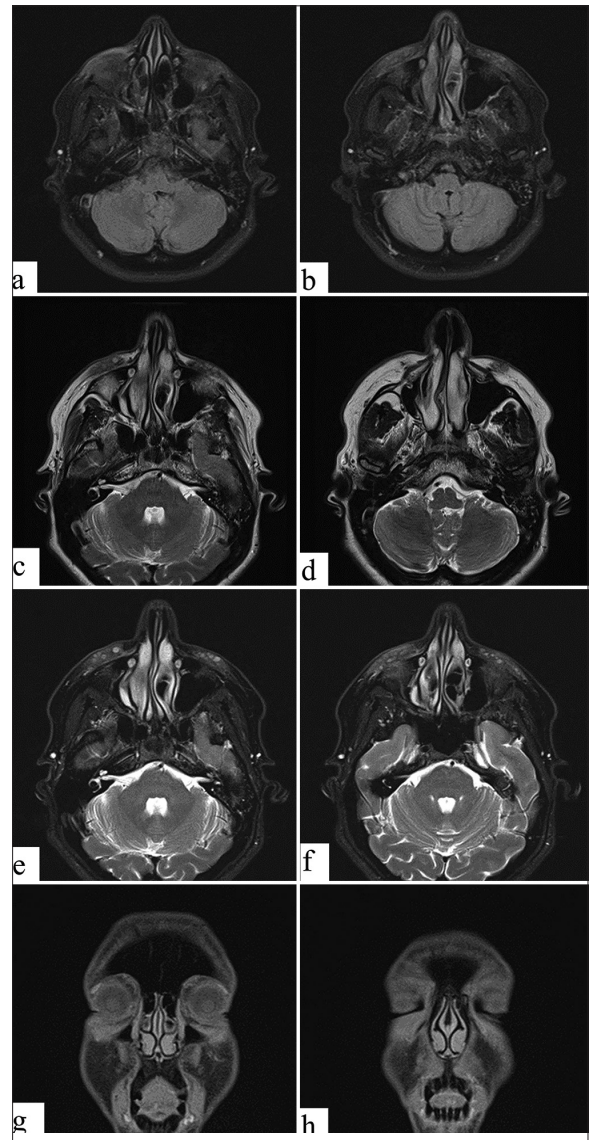


Figure 2: Magnetic resonance imaging. (a and b) Axial fluid-attenuated inversion recovery images showing bilateral cosmetic material injection (fillers) injection seen within the maxilla and nasolabial folds with mild contour asymmetry, being larger on the right. (c and d) Axial transverse relaxation time (T2) images show bilateral tiny multiple foci of high T2 signal rounded material, multiple and more on the left side, being larger on the right. (e and f) Axial T2 Dixon images showing bilateral tiny multiple foci of high T2 signal rounded material, as described above. (g and h) Coronal longitudinal relaxation time (T1) Dixon images showing bilateral tiny multiple foci of intermediate to low T1 signal rounded material, as described above. No evidence of localized collection, distal migration, granulomatous changes, fibrotic changes, or scars.

Table 1: Summary of patients with delayed inflammatory reactions to hyaluronic acid dermal filler following COVID-19 vaccination.

Sex, age History	Site of filler	Duration of filler	Type of vaccine	Delay of reaction	Clinical features	Treatment	Treatment response
Munavalli et al. ¹³ F, 43 Prior history of idiopathic urticaria	Temples, cheeks	2 years	2 nd dose Pfizer BNT162b2	2 days	Moderate swelling in the periorbital area, and the medial and lateral cheeks.	5 mg of Lisinopril (5 days)	Back to baseline after 2 days
F, 31 prior history of a filler reaction (edema following a respiratory infection)	Earlobes Bilateral malar cheeks, nasolabial folds Nasolabial folds	27 months 19 months 7 months	2 nd dose Moderna	24 h	Swelling of the upper mucosal lip, the left earlobe, and bilateral zygomas	5 mg of Lisinopril (2 days) 10 mg of Lisinopril (3 days)	Minimal effect Back to baseline
F, 36	Tear troughs, lips	13 months	1 st dose Moderna	18 h	Edema in the infraorbital and perioral regions, in the upper lip Swelling and inflammation expanded to the mid-cheeks	Cetirizine (20 mg) 5 mg of Lisinopril (3 days)	No improvement Improvement after 6 h, back to baseline at 24 h
F, 76 prior history of a filler reaction	Cheeks	10 months	1 st dose Pfizer	10 days	Panfacial and periorbital swelling.	5 mg of Lisinopril (7 days)	Improvement within 4 days, back to baseline at 7 days
F, 39 No history	Tear trough	6 months	1 st dose Pfizer	2 days	Tender, erythematous swelling at her left tear trough area.	Watchful waiting	Spontaneous resolution by day 5
F, 61 No history	Pan facial (chin, jawline, periorbital)	10 months	1 st dose Pfizer	Few days	Intermittent facial swelling, mainly at the cheeks and under eye	Hyaluronidase	Complete resolution 48h after injection
F, 45 No history	Chin, lips	10 months	2 nd dose Pfizer	24 h	Swelling at the injection sites	Lisinopril 5 mg daily (7 days)	Improvement within 24h Complete resolution after 72h

(Contd...)

Table 1: (Continued).

	Sex, age History	Site of filler	Duration of filler	Type of vaccine	Delay of reaction	Clinical features	Treatment	Treatment response
Savva <i>et al.</i> ¹²	F, 38 No history	Lips	1 month	1 st dose Pfizer 2 nd dose Pfizer	2 days 2 months	Small erythematous nodules on lips mildly painful Painful erythematous edema on both lips	Methylprednisolone (8 days)	Spontaneous resolution after 7 days Complete resolution 5 days
Calvisi ⁹	F, 60 No history	Lips	1 year	1 st dose Pfizer (after 2 prior doses of AstraZeneca) 3 rd dose Pfizer	5 days	Swelling in the upper lip	Watchful waiting	Spontaneous resolution after 3 days
	F, 45 No history	Lips	2 years			Angioedema in the upper lip	Prednisolone 25 mg for 3 days	Complete resolution after 3 days
Beamish <i>et al.</i> ⁷	F, 40 No history	Nasolabial folds	5 months	1 st dose Moderna (after 2 doses of Pfizer)		Erythema and edema at the site of injection	Watchful waiting	Spontaneous resolution after 7 days
	F, 23 No history	Malar eminences, lips, jaw, and chin	1 year	2 nd dose Pfizer	6 weeks	Painful asymmetric swelling over her maxilla, lips, and lower jaw	Single dose of IV diphenhydramine 50 mg Single dose of IV dexamethasone 10 mg Oral prednisone	Moderate symptomatic improvement and nodule regression.
Azzouz <i>et al.</i> ⁶	F, 43 HCTD, Hashimoto's thyroiditis, and craniopharyngioma	Multiple facial skin folds	3 months	2 nd dose of Moderna (3 weeks before injection)	24 h	Facial edema nodules and indurations on her cheeks and chin, at the sites of previous HA injections	Local steroid injections Hyaluronidase injections	
Neamatallah ⁸	F, 36 No history	lips	22 months	1 st dose Pfizer 2 nd dose Pfizer	3 days 12 h	Dryness, induration, and erythematous swelling in the lower lip	Watchful waiting hyaluronidase and triamcinolone injection	Symptoms reduced within two weeks improvement in the following days

(Contd...)

Table 1: (Continued).

	Sex, age History	Site of filler	Duration of filler	Type of vaccine	Delay of reaction	Clinical features	Treatment	Treatment response
Ortigosa et al. ¹¹	F, 35 No history	Malar, and chin regions lips, nasojugal furrow	5 years 16 months	1 st dose AstraZeneca	24 h	Induration and edema in her lips and chin	Oral prednisone (total of 21 days) hydroxyzine (50 mg/day)	Improvement was achieved, persistence of mild lip edema.
	F, 47 No history	Around the eye	18 months	2 nd dose Pfizer	4 weeks	Edema in the lower eyelids Recurrence	Prednisolone 20 mg/day for 4 days Lisinopril 5 mg	Complete resolution after 7 days Resolution in 24 h
F, 34 No history	F, 56 No history	Lips	10 months	3 rd dose of Pfizer	24 h	Pain and mild edema in the lips	Loratadine 10 mg/day for 2 days	Complete resolution in 72 h
		Mandibula (jaw angle), chin and lips		1 st dose Pfizer	48h	Induration and edema in the mandible and chin	Oral prednisone 20 mg twice a day for 3 days	Complete resolution was achieved
F, 43 No history	F, 29 No history	Nasolabial folds and lips	1 year 15 days	2 nd dose AstraZeneca	7 days	Edema, erythema, increase in the temperature of her lips	Ibuprofen 40 mg/day and prednisone 40 mg/day (tapered for 3 weeks)	Symptoms reduced after 7 days
		Lips	4 months	1 st dose Pfizer		Swelling of the lips and the bilateral under-eye compartments	Watchful waiting Hyaluronidase injection (under-eye)	Lip swelling had resolved, but the inflammation around her eyes persisted
Osmond and Kenny ¹⁴	F, 26 No history	Chin and jaw	3 years	2 nd dose Moderna	24h	Chin swelling	Watchful waiting	Complete resolution in 1 day symptoms gradually resolved in 48 h

HCTD: Hereditary connective tissue disorder, HA: Hyaluronic acid

reactions such as erythema, bruising, itching, injection site infections, lumps, and migrations due to technique errors and type I hypersensitivity reactions, which typically occur within minutes or hours of injection due to an immunoglobulin E-mediated immune response such as angioedema or anaphylactic reactions.¹⁶ Delayed reactions may occur weeks, months, or years after the initial injection and are characterized by induration, erythema, and edema in the injection site.¹⁷ The incidence rate of DIRs to HA soft-tissue fillers varies considerably between products, ranging from 0.02% to 4.25%.^{16,17}

The full extent of the mechanisms involved in DIRs remains to be fully elucidated. Several triggers for DIRs have been suggested, including systemic infection, vaccination, local trauma, injection technique, product quality, filler volume, and previous or current dental procedures.¹⁷ Biofilm formation has also been implicated, but its role remains unclear.^{16,17} Both filler characteristics and host immune status appear to play a role in activating certain mechanisms leading to DIRs. Immune-mediated type IV hypersensitivity to fillers in patients with DIRs has been investigated in a case report by Azzouz *et al.* intradermal testing with 0.1 mL of suspected HA filler was performed and showed an inflammatory nodule within 2 weeks of application.⁶ However, according to the group consensus by Artzi *et al.*, it is unclear whether DIRs should be considered as true hypersensitivity reactions.⁴

To date, DIR to COVID-19 vaccination was reported in 21 patients [Table 1]. All patients were female, and the mean age was 42.19 (range: 23–76 years). The mean interval between filler injection and reaction was 15.93 months (range: 0.5–60 months). Eleven developed symptoms after the first dose of vaccination, 10 after the second dose, and two after the third dose. The mean time interval between the vaccine injection and the DIR to filler was 8.96 days (range: 1–60 days). Fourteen patients developed symptoms after injection of the mRNA Pfizer-BioNTech vaccine, of which 6 after the first dose, 4 after the second dose, two after the third dose, and two exhibited symptoms both after the first and second dose. Five patients developed symptoms after injection of the mRNA Moderna vaccine, of which two after the first dose and three after the second dose. Two patients developed symptoms after injection of the AstraZeneca vaccine, of which one was after the first dose and one after the second dose. Given its rarity, it is unclear whether DIR is associated with a specific type of HA filler. In our patient, the reaction appeared 3 days after receiving the second dose of the mRNA Pfizer-BioNTech COVID-19 vaccine at the site of HA filler injection (8 months earlier).

The exact mechanism of DIR to COVID-19 vaccination is still not fully understood. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into host cells is mediated by its spike glycoprotein and binds the

angiotensin-converting enzyme receptor 2 (ACE2) as the cellular receptor. Membrane-bound and soluble ACE2 catalyzes the conversion of the proinflammatory angiotensin II (AngII) to the anti-inflammatory metabolites angiotensin 1–7.¹³ The receptor-binding domain of the COVID spike protein irreversibly binds to membrane-bound ACE2, initiating membrane fusion and entry into the cell, effectively down-regulating ACE2 and its ability to locally control AngII.¹⁶ Accumulation of AngII upregulates the expression of monocyte chemoattractant protein type 1, tumor necrosis factor-alpha, interleukin 6, and interleukin 8, which are potent chemoattractants and activators of neutrophils and has been shown to upregulate cluster of differentiation 44 (CD 44) glycoprotein. CD44 glycoprotein has an affinity for binding free extracellular HA, particularly low molecular weight (LMW) HA, inciting a cluster of differentiation 8 (CD8) + The T helper cells (Th1) immune response.¹³

The role of AngII in DIR to COVID-19 vaccination could explain the efficacy of ACE inhibitors like lisinopril for the treatment of this DIR. ACE inhibitors reduce the AngII levels, thereby mitigating the effects of rising spike protein levels and, additionally, reducing AngII -induced aldosterone secretion by the adrenal cortex, which leads to an increase in sodium excretion and, subsequently, an increase in water outflow.

Seven patients were treated with lisinopril and showed rapid improvement and complete resolution of symptoms in 1–7 days [Table 1]. Lisinopril usually reaches peak efficacy within 6 h after oral intake, as seen in our patient, who experienced significant improvement 6 h after the first dose. 5 mg of lisinopril is a good starting dose for the treatment of DIRs, escalating to 10 mg if a partial improvement is seen. The suggested duration of therapy is 3–5 days or at least 1–2 days after the swelling subsides. Lisinopril is usually well tolerated, but clinicians should be aware of its adverse effects, such as hypotension, cough, and head and neck angioedema.^{5,13}

CONCLUSION

The COVID-19 pandemic has seen a remarkable decline and the wave of mass vaccination has passed. It is clear that the benefits of vaccination far outweigh the risk of cutaneous DIR. Nevertheless, with the ever-increasing demand for dermal filler treatment, clinicians should be mindful of the risks of this reaction and its potential etiologies. Further studies are needed, especially with the emerging use of ACE-I for the prevention and treatment of DIRs to HA fillers.

Authors' contributions

Conceptualization: Noureddine Litaïem, Mariem Fazzani. Methodology: Noureddine Litaïem, Mariem Fazzani, Abdulmooti Hawilo. Writing - original draft preparation: Mariem Fazzani. Writing - review and editing: Noureddine

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Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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