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Hyaluronic acid soft tissue filler delayed inflammatory reaction following COVID-19 vaccination – A case report

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Abstract

Background: The use of hyaluronic acid soft tissue fillers in aesthetic medicine exploded in recent years for many reasons, including being relatively safe. Incidence of delayed inflammatory reactions (DIRs) to hyaluronic acid soft tissue fillers range between 0.3% and 4.25%. These reactions are mediated by T-lymphocytes and can be triggered by flu-like illnesses, including SARS-CoV-2 infection. Vaccination may also induce hypersensitivity.

Aim: In this case report, we present two cases of delayed reaction after hyaluronic acid soft tissue filler treatment of the tear trough area and following mRNA vaccination against SARS-Cov-2, also known as COVID-19, months later.

Patients: A 39-year old female who previously had her tear trough area treated with hyaluronic acid soft tissue filler developed swelling days after getting the mRNA Pfizer-BioNTech COVID-19 vaccine. Another patient, a 61-year-olf female, developed intermittent facial swelling in areas previously treated with hyaluronic acid soft tissue fillers days after receiving her first dose of the mRNA Pfizer-BioNTech COVID-19 vaccine.

Results: As demonstrated in our case report, vaccination against COVID-19 may induce DIRs in patients who previously had hyaluronic soft tissue fillers.

Conclusion: Delayed inflammatory reactions to hyaluronic acid soft tissue fillers are uncommon and usually self-limited, with frequent spontaneous resolution. However, considering the ongoing pandemic and the worldwide demand for vaccines against COVID-19, the aesthetic providers should be conscious of the risks posed by the interaction of such vaccines in patients who previously had or seeking hyaluronic acid soft tissue filler injections.

KEYWORDS
dermal filler, filler, hyaluronic acid, hypersensitivity, immunology, intradermal injection

1 | INTRODUCTION

The use of hyaluronic acid (HA) soft tissue fillers for noninvasive aesthetic procedures is becoming prevalent. In 2019, over 4 million HA soft tissue filler procedures were performed worldwide, an increase of 15.7% from 2018, ranking second as the most sought nonsurgical treatment.[1] HA fillers have been shown to have an excellent safety profile while delivering significant results in facial rejuvenation with high patient satisfaction.[2,3]

The ideal soft tissue filler should have many properties, including being safe, biocompatible, biodegradable, effective, practical, versatile, nonmigratory, non-carcinogenic, predictable, cost-effective, and stable.[4] HA is immunologically inert, and adverse reactions with HA filler, acute or late-onset, are considered rare.[4–7]

Acute type 1 hypersensitivity reactions, occurring within minutes or hours, are immunoglobulin E (IgE)-mediated. Conversely, late-onset or delayed reactions are inflammatory, T-cell lymphocytes responses and may present as tender and erythematous swelling or nodules.[8–10] Various factors may contribute to HA soft tissue filler delayed reactions, many reporting a flu-like illness before the delayed reactions, including influenza and SARS-CoV-2.[4,9,11,12] The latter is also known as COVID-19.

Recently, after an international survey on 106 participants, the global recommendation on COVID-19 vaccines and soft tissue filler reactions, in cooperation with the international society of dermatologic and aesthetic surgery, concluded that there is no evidence for concern of developing soft tissue filler-related reactions following COVID-19 vaccination.[13]

In this case report, we will present two patients who presented with a delayed-type inflammatory reaction within days after receiving a first dose of the mRNA Pfizer-BioNTech COVID-19 vaccine.

2 | CASE REPORT

2.1 | Case 1

A 39-year old female, physically fit and healthy, and without any medical comorbidities nor allergies, had her tear trough injected with an HA soft tissue filler, Juvéderm Volite (Allergan inc.), in October 2020 by the author for the correction of undereye hollowness. The placement was done in the subdermal plane using a microcannula, 25 G × 38 mm, TSK Steriglide, under proper sterile condition. A total of 0.8 ml of HA filler was injected into her left tear trough and 0.5 ml to her right tear trough in two separate treatment sessions. The procedures were uneventful.

In April 2021, 2 days after receiving the first dose of the mRNA Pfizer-BioNTech COVID-19 vaccine, she reported tender, erythematous swelling at her left tear trough area. The patient contacted the author's clinic. On day 1, a selfie-type picture of the reaction was taken for documentation by the patient. (Figure 1). She also experienced flu-like illness symptoms, including fatigue, headache, myalgias, and anorexia, which resolved within 4 days.

The following day, a complete medical history was taken. There was no history of recent trauma and infection, and she has not been taking any medications. She was well before getting the vaccine. On exam, the left tear trough area was swollen, mildly erythematous, and tender to touch (Figure 2a). There was no palpable nodule and fluctuant mass. The patient reported that the area was slightly better than the previous day. The facial right side was without abnormalities. A watchful waiting approach was therefore taken. Her adverse reaction resolved spontaneously by day 5 (Figure 2b) without any intervention.

2.2 | Case 2

A 61-year-old female patient, physically healthy, without allergies or significant medical history, except for intermittent benign vertigo,

FIGURE 1 Patient's own photograph (taken from a mobile device) on day 1 of appearance of signs and symptoms, showing swelling and related Tindall effect over the left tear trough area

had in June 2020 pan facial injections by the author. Placements of soft tissue fillers were as follow: deep supraperiosteal injection of Juvéderm Voluma (Allergan Inc.) at the zygomatic arch with a 30G ½ inch TSK needle for a total of 0.3ml per facial side, and lateral and medial SOOF were injected with the use of a microcannula 25 G × 38mm TSK Steriglide, 0.7 ml per side. Juvederm Volux (Allergan Inc.) was injected deep supraperiosteal at the chin and jawline using a 27 G needle ½ inch TSK for a total of 2 ml. The following products were injected using a microcannula 25 G × 38 mm TSK Steriglide: Juvéderm Volift (Allergan Inc.) was injected subdermal at the palpebromalar groove for a total of.5 ml per side, and Juvederm Volbella (Allergan Inc.) was used for the correction of the tear trough deformity for a total of.5 cc per side. The procedure was done under proper sterile condition and was uneventful.

In April 2021, the patient had the first dose of the mRNA Pfizer-BioNTech COVID-19 vaccine. A few days later, she developed flu-like illness symptoms, as can be expected with the vaccine. However, the patient also reported of experiencing intermittent facial swelling that would come and go, lasting a day or so on average per episode. Swelling could be on either side of the face, localized primarily at the cheeks and undereye where she had the soft tissue fillers previously injected. We examined her 3 weeks after she had her vaccine, as that day, she experienced left undereye swelling that was worse than the previous episodes and persisted beyond 72 h. The patient did take a photograph using a mobile device for documentation (Figure 3). On exam, the area was soft, mildly tender with definite swelling, but without erythema, nodule or mass (Figure 4). The author decided

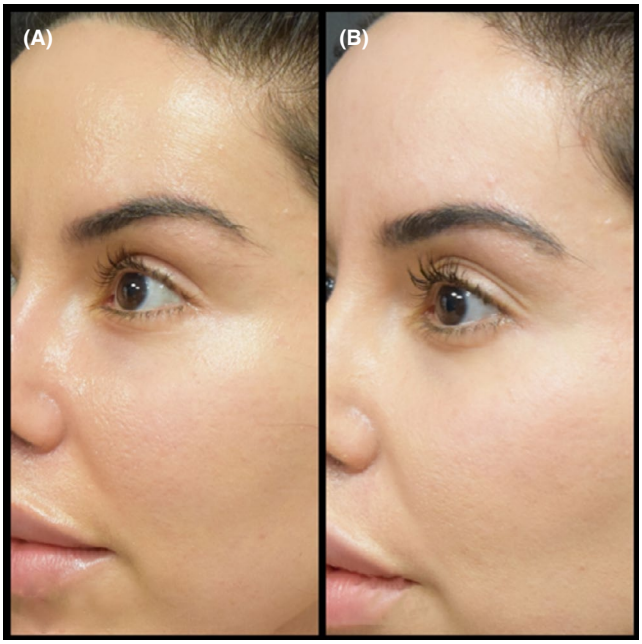

FIGURE 2 Photographs taken on the day the patient presented to the author's clinic (2a) and at the follow-up visit (2b) 4 days after. We can appreciate the spontaneous resolution of the delayed inflammatory response

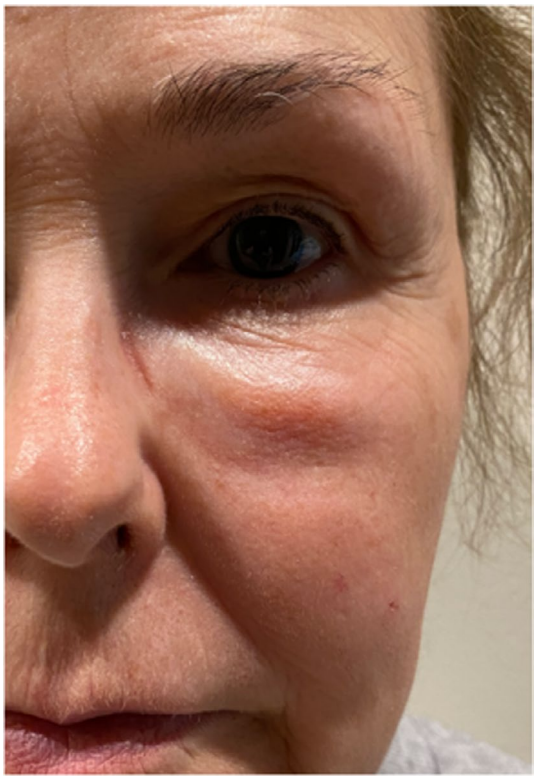

FIGURE 3 Patient's own photograph (taken from a mobile device) on day 2 of appearance of signs and symptoms, showing infraorbital swelling where soft tissue fillers were previously injected

to dissolve the product with 75 units of hyaluronidase at a concentration of 150 units/ml. She experienced improvement the following day to complete resolution by the time we examined her for a follow-up 48 h after the hyaluronidase injection (Figure 5). She reported no recurrence of swelling until now.

3 | DISCUSSION

Recently, a team of experts defined the duration of delayed inflammatory reactions (DIRs) as reactions occurring after a normal state, 2–4 weeks or longer after injections.[14] Although the experts strongly supported an infectious trigger, viral or bacterial, for many of the cases reported, they rejected the word hypersensitivity for a broader definition and opted for inflammatory. They confirmed other potential triggers of DIRs, including but not limited to previous or recent dental procedures, low-quality products, and improper techniques. Clinically, DIRs after HA filler were defined as discoloration, erythema, localized hardening of tissue, painful nodules, and edema.[14]

Hyaluronic acid fillers are nonpermanent and they last on average between 3 and12 months and even longer in some patients.[15,16] It was recorded by magnetic resonance imaging that soft tissue fillers could be detected as long as 12 years. Notably, most patients denied having soft tissue fillers treatments when the last injections were over 2 years.[17] Recollection difficulties of previous procedures by patients may be an obstacle in diagnosing, reporting, and treating DIRs if they occur. Hence, the need for appropriate documentation and more accessible retrieval of medical information. Furthermore, newer, longer lasting HA fillers with improved cross-linking technologies could potentially be seeds for inflammation and increase the rate of DIRs.

DIRs to HA fillers are bothersome for patients and can be challenging for the aesthetic practitioner. However, it is infrequent. Recent literature reports revealed an incidence rate ranging from 0.3% and up to 4.25% for Juvederm Volbella.[4,8,18,19] This raises the possibility that newer family of soft tissue fillers may be more prone to DIRs. Interestingly, the authors of another study noted within a year a lower incidence of 1.0% per patient for Juvederm Volbella and reported no delayed reactions with Juvederm Vollure (also known as Juvederm Volift) and Voluma, also utilizing the vycross technology. Conversely, NASHA technology-made soft tissue fillers have an incidence rate of DIRs reported at 0.3% and hypersensitivity reactions at 0.8%.[8]

The full extent of the mechanisms implicated in DIR has yet to be fully elucidated. It can present weeks to months after the procedure, and many cases were shown to have an identifiable immunological trigger.[4,14] In their prospective chart reviews on 4,702 treatments, Beleznay et al. noted a flu-like illness in 39% of patients who presented with delayed-onset nodules with an incidence of 0.5% for Juvederm Voluma.[4] A case series, on 14 patients with a history of soft tissue filler injections, described erythematous and painful swelling a few days after the beginning of a flu-like illness.[11]

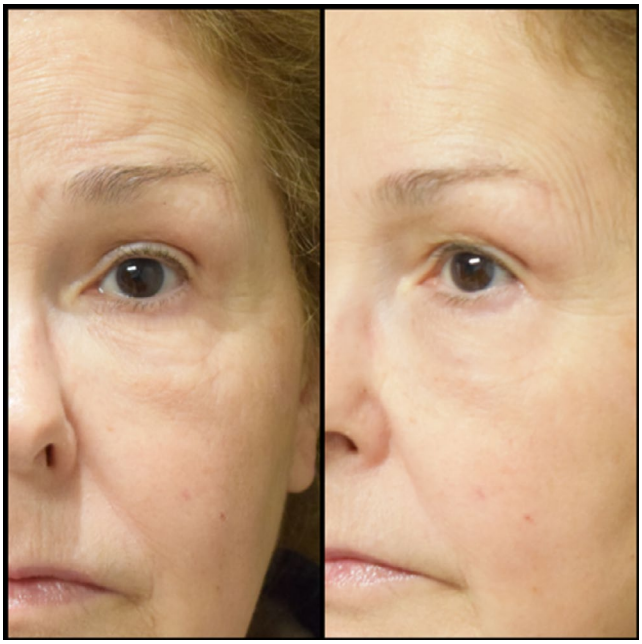

FIGURE 4 Photographs taken the day the patient presented to the author's clinic, showing persistent infraorbital swelling

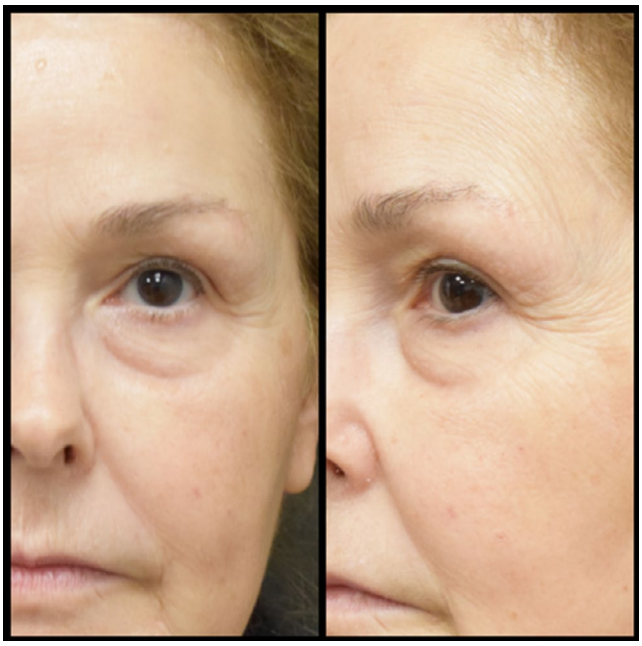

FIGURE 5 Photographs taken 48 h after one single injection session of 75 units of hyaluronidase. We can appreciate complete resolution of the swelling

High molecular weight HA is known for its anti-inflammatory effects, as low molecular weight (LMW) HA of less than 20 kDa was demonstrated to be pro-inflammatory.[20–22] After soft tissue filler procedures, LMW HAs are present due to degradation and as well as a cross-linking component.[4,23,24] Macrophages and dendritic cells are activated by LMW HA and it signals T cells via CD44 cell surface receptors.[21,25] It was postulated by Beleznay et al.[4] that systemic inflammatory responses might accelerate the degradation of LMW HA from acute free radical production influencing CD44-HA signaling and resulting in DIRs. This process is also believed to be the cause of soft tissue filler swelling seen after SARS-CoV-2 infection.[12]

Recently, Munavalli et al.[26] proposed a mechanism related to the angiotensin-converting enzyme receptor (ACE-2). They theorized that COVID-19 mRNA vaccines would potentially decrease the conversion of the pro-inflammatory angiotensin-II (ANGII) present in the skin. Therefore, the increased level in ANGII would stimulate inflammation and immune response by activating CD8+ and TH1, respectively, and resulting in the DIRs as seen in this case report.[19,26]

4 | PREVENTION AND MANAGEMENT

Because it is not always possible to find the exact cause of DIRs, prevention can be quite challenging. However, to prevent adverse reactions, including biofilm formation, it is essential to remove makeup before injections, removing hair and pieces of jewelry in proximity to the treating areas, and clean the skin thoroughly with an antimicrobial solution. Proper techniques should be used to prevent contamination of the injection sites or implanting contaminants. Also, injections should be delayed if there are any signs of infection or inflammation in the proximity of the treatment area (including ear, nose, throat, and dental infections) or recent dental work, cosmetic procedures, and vaccination.[27] We recommend waiting for 3 weeks after the COVID-19 vaccine before treating patients with soft tissue fillers, as it may take up to 21 days for the peak immune response.[28] Furthermore, it is argued that larger boluses of HA filler may contribute to nodule formation. Hence, as a precautionary measure, it is recommended to inject a smaller volume with every session of HA filler.[4,29]

DIRs are often transient, self-resorbing within days to weeks; thus, intervention is not always necessary. When a nodule is present, small in size (less than 0.5 cm) and without pain, or minimal, a watchful waiting approach is recommended. In contrast, intervention is necessary if nodules are not improving, painful and tender, with edema and erythema.[14] Nodules are often inflammatory in nature, but keeping the possibility of an infection process, including biofilms and atypical organisms, in the differential diagnosis is important.[30] If the presence of a fluctuant mass is noticed, cultures should be sent for aerobic and anaerobic bacterial, mycobacterial, and fungal cultures before treatment. A biopsy can also be performed if there is no resolution following treatment. [4,30–32] Imaging and blood test evaluating inflammatory markers like C-reactive protein might be helpful with the diagnosis.[8,33]

As for the treatments of DIRs, antihistamines were found to have limited value.[9,10] Noninflammatory nodules that are visible may be dissolved with hyaluronidase (HYAL).[7] In more severe cases of DIRs, which intervention to perform first is debatable. Beleznay et al.[4] frequently treated delayed nodules from Juvederm Voluma with oral and or intralesional steroids combined with HYAL injections. They

believed primarily that these nodules were immune-mediated. However, systemic steroid therapy may also interfere with the immune response necessary to combat an infection or develop adequate immunity, making its role questionable during the current COVID-19 pandemic and large-scale related vaccination.[34] However, It is generally recommended to start with antibiotic treatment, either tetracycline or a macrolide, for 3–6 weeks.[7,14] Also, nonsteroidal anti-inflammatory drugs can be prescribed in mild cases. Mild to more intense reactions should be treated with HYAL, with 10 units of HYAL per.1 ml of HA filler or about 30–300 units per nodule. For the latter, needles are preferred to break and penetrate the encapsulated filler.

Secondary therapies involve the use of intralesional steroid, alone or in combination with 5-FU. Infection with fluctuating mass should be treated with antibiotics, incision, and drainage.[7,14] It is the author's experience and the recommendation of others that retreatment is definitely possible once DIR resolves. Recurrence of a DIR is possible and should be clearly communicated with the patients.[4,14] A skin test should also be performed with 0.1 ml of HA prior to an entire treatment session.

A novel treatment of DIR to HA fillers following COVID-19 vaccination using oral angiotensin-converting enzyme inhibitors (ACE-I) was recently published by Munavalli et al.[26] They presented four cases where all patients responded rapidly to a low dose of oral Lisinopril, an ACE-I. They believe that ACE-I therapy reduces the immunoglobulin response to SARS-COV-2 spike glycoprotein and helps downregulate CD44 by inhibiting the pro-inflammatory angiotensin-II. This therapy was shown to be beneficial in the treatment of other cutaneous disorders, including hypertrophic scars and keloids, systemic scleroderma, psoriasis, and dystrophic epidermolysis bullosa.[35] Tolerability to Lisinopril is relatively excellent, and a dose of 10 mg for 3–5 days is recommended for isolated cases of DIR related to COVID-19.[26] Until further research confirm the efficacy and safety of ACE-I, the author's recommended treatment approach specifically for COVID-19 vaccination-related DIRs to HA soft tissue fillers is highlighted in Table 1.

Our cases resolved entirely and without minimal intervention. The first case presented resolved spontaneously without any treatment, and the second case soon after the injection of hyaluronidase. Given that the patients were perfectly fine before receiving the mRNA COVID-19 vaccine, and presented with localized edema within days after their immunization, a diagnosis of delayed inflammatory response secondary to the mRNA COVID-19 vaccine was concluded. No other triggers were found, including infection, trauma, dental or medical procedures etc. Biopsy and histological analysis were not performed as judged unnecessary by the author.

TABLE 1 Author's First-Line Therapies

Watchful waiting approach.
Hyaluronidase intralesional (10 units of hyaluronidase per 0.1 ml of soft tissue filler; can be repeated as needed, wait at least 48 h).
Oral prednisone 40 mg daily for 5–7 days (Consider a longer treatment duration with a tapering dose for slowly resolving, or recurring DIRs).

5 | CONCLUSION

The delayed-type inflammatory reactions seen in this case report are likely to be immunologically related to the interaction of the mRNA COVID-19 vaccine received and HA soft tissue fillers.

Due to the ongoing popularity of HA soft tissue fillers and as the rate of COVID-19 infections is increasing around the world, including the escalation of vaccination against SARS-CoV-2, delayed inflammatory reactions cases related to HA soft tissue fillers are likely to become prevalent. These reactions are presumptively due to the activation of CD44 by LMW HA, causing a risk of hypersensitivity for patients who did receive HA soft tissue fillers.

However, due to the morbidity, mortality, and socioeconomic impact of the COVID-19 pandemic, vaccination should not be discouraged.[36–38] Importantly, many DIRs triggered by an immunological process are localized and self-limited with frequent spontaneous resolution.[4] Also, DIRs to HA soft tissue fillers are relatively rare and should not be a deterrent for receiving the COVID-19 vaccine.[4–7]

Aesthetic practitioners should be mindful of the risks discussed in this case report. Patients seeking HA soft tissue filler must be educated and correctly consented about the risk of DIRs related to COVID-19 infections and vaccines prior to treatment. Further studies are needed, especially with the novel use of ACE-I medication to prevent and treat DIRs related to HA filler and COVID-19.

CONFLICT OF INTEREST

None.

ETHICAL APPROVAL

The patients gave their written consent for their images to be used for this publication. Ethical approval was not sought for the present manuscript because it was not required.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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