

# Delayed Inflammatory Reactions to Hyaluronic Acid Fillers: A Case Series of Novel Associations

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## ABSTRACT

**Background:** Delayed reactions to hyaluronic acid (HA) fillers have been reported following various immunologic and infectious triggers.

**Aim:** Herein, we describe cases of delayed immunologic reactions (DIRs) following HA-soft tissue augmentation fillers precipitated by triggers not previously described in the literature.

**Patients:** Case 1 describes a 57-year-old female with DIR to HA-filler following a motor vehicle accident in the marionette lines and nasolabial folds. Case 2 is a 54-year-old female who had a filler-related DIR following an episode of contact dermatitis shortly after laser resurfacing. Finally, in Case 3, we diagnosed a 54-year-old female with DIR to HA-filler on the hands following prolonged gardening without gloves.

**Conclusion:** DIRs are an important filler-related complication. Practitioners need to be aware of the variable clinical presentations and a wide array of triggers. Given that these may not always be preventable, it is important for patients to understand the risk of DIRs, albeit low.

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## INTRODUCTION

Hyaluronic acid (HA) fillers have become increasingly popular in non-surgical rejuvenation procedures. They are easy to administer and help in addressing various cosmetic concerns, making them a popular option among practitioners. Moreover, their reversible nature and excellent safety profile have led to increased use.

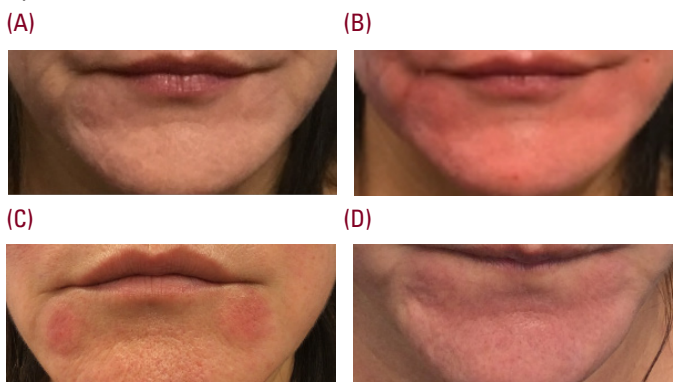
Immune reactions are uncommon but well-described following HA-fillers and can be either immediate or delayed. Delayed immune reactions (DIRs) may present as nodules, edema, and/or erythema. Various triggers for DIRs have been described. Herein, we add to the literature three cases of DIRs to HA-fillers: one triggered by a motor vehicle accident, one following significant plant exposure while gardening without gloves, and another following an episode of contact dermatitis after laser resurfacing.

### Case 1

A 57-year-old woman with phototype-IV skin presented to our clinic on May 2<sup>nd</sup>, 2018, concerned about volume loss and facial aging of the lower third of the face. She had deep wrinkles in the marionette lines and oral commissures, with mildly prominent nasolabial folds. Her medical history included osteoarthritis and herpes simplex. She had no drug allergies or history of autoimmune disease.

Based on her cosmetic goals, 1 mL of Restylane® Refyne was injected in the nasolabial folds and marionette area, and 1 mL of Restylane® Defyne was injected in the secondary smile lines following three rounds of disinfecting with alcohol and chlorhexidine-based solution. The injection of these HA fillers was performed in a deep subdermal plane. Areas of filler placement were subsequently molded and massaged to minimize clumps. No visible or palpable nodules were present upon discharge (Figure 1A and 1B).

**FIGURE 1.** (A) Photograph prior to filler. (B) Immediately following filler in the marionette lines, nasolabial folds, and smile lines. (C) Erythema and swelling at the marionette lines 3 months following a motor vehicle accident. (D) Improvement of erythema and swelling following hyaluronidase.



Two weeks later, the patient was involved in a motor vehicle accident, sustaining multiple injuries, including concussion and abrasions over the head, neck, trunk, and extremities. Notably, she did not have an infection and was not treated with antibiotics. Extensive exposure history otherwise revealed no recent dental procedures, vaccines, or infections preceding the flare.

Photos immediately following the accident while in urgent care revealed no erythema or swelling of the face. However, in the weeks that followed, she developed increasing swelling at the sites of prior filler injections. On follow-up 8 weeks after the accident, she had persistent redness and swelling over the marionette area and nasolabial folds (Figure 1C).

DIR to HA filler was diagnosed, which is suspected to have been triggered by physiologic stress and skin barrier compromise from minor abrasions following a motor vehicle accident. The patient opted for filler dissolution, and 50 units of Hylenex® (hyaluronidase) was administered to each side (Figure 1D).

## Case 2

A 54-year-old woman with phototype-II skin presented to our clinic on August 28<sup>th</sup>, 2023, for recommendations to improve texture and dyschromia on the chest, as well as fine etched lines and sebaceous skin on the face. Several months prior to consultation with us, she had filler injected infraorbitally as well as in the cheeks at another facility (Juvéderm Voluma® in both areas). She had no known drug allergies, and her past medical history was otherwise unremarkable.

At our clinic, she underwent a session of a fractional ablative erbium laser for the face as well as a hybrid ablative and non-ablative fractional laser for the chest and neck. Following treatment, platelet-rich plasma was applied over the full face in a sterile manner. Post treatment instructions were given: regular use of a post-procedure cleanser (Don't Be So Sensitive®), dilute hypochlorous acid (HypoCyn®), and regular use of post-treatment petrolatum, in addition to maintaining good facial hygiene.

On follow up 2 days later, she was noted to have increasing redness and itching in the treated areas. On examination, there was uniform, well-demarcated erythema over the face, with no bumps, pustules, or drainage (Figure 2A). The cleanser was discontinued and switched to a Vanicream® cleanser, and she was started on doxycycline empirically. The dilute hypochlorous acid and white petrolatum were continued. The following day, she reported that her symptoms had significantly improved up until she re-applied the HypoCyn® product. She was advised to discontinue this hypochlorous acid antimicrobial product, and her symptoms and redness resolved over the following two days. Bacterial cultures taken prior to initiation of antibiotics were negative.

**FIGURE 2.** (A) Sharply-demarcated erythema and swelling on the face at the site. (B) Swelling and erythema at the site of prior infraorbital filler placement following laser treatment and suspected contact dermatitis.



Given the significant itching, sharp demarcation of erythema, temporal association with topical product use, and rapid resolution following discontinuation, we suspect that the patient had an irritant contact dermatitis secondary to the hypochlorous acid product, likely provoked in the setting of a compromised skin barrier following laser therapy.

Notably, at the day 2 post-laser follow-up visit, the patient had pronounced erythema and swelling of the infraorbital area at the sites of the previous filler injection. Although the redness from the suspected contact dermatitis resolved within a few days, the infraorbital erythema and swelling persisted for weeks afterward (Figure 2B). We suspect the patient had a filler-related DIR following an episode of contact dermatitis after laser resurfacing.

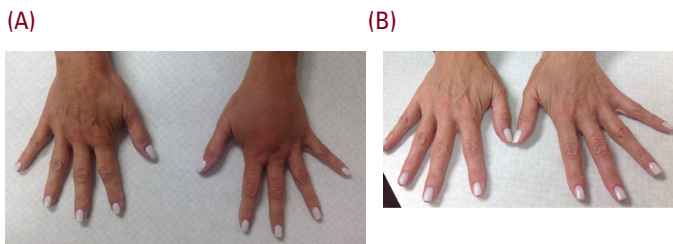
## Case 3

A 54-year-old woman with phototype-III skin presented to our clinic in March 2016 for treatment of aging of the dorsal hands. On examination, she had mild volume loss and signs of photoaging on the dorsal hands bilaterally with slightly visible veins. She had no medical conditions and no known drug allergies or autoimmune diseases.

As part of a clinical trial, she had Restylane® Lyft filler injected in the left dorsal hand, which was well tolerated. Three months later, she presented to our clinic for follow up for swelling, itching, and soreness of the left hand that had progressed over two weeks. Exposure history was reviewed in detail, revealing no recent dental procedures, vaccines, or infections. After detailed discussions with her and her husband, it was elucidated that she had been gardening without gloves 2 days prior to the onset of the swelling.

On examination, exhibited non-pitting edema over the left dorsal hand at the filler injection sites, without any erythema, tenderness, or fluctuance (Figure 3A). She had no fevers or chills and felt otherwise well. Notably, she had HA filler to the eyelids and lips six months prior, which were also now swollen.

**FIGURE 3.** (A) Erythema and non-pitting edema of the left dorsal hand three months following HA-filler (no filler was injected to the right hand). (B) Resolution of DIR following treatment with hyaluronidase and prednisone.



We diagnosed DIR to HA filler triggered by transient bacteremia due to minor abrasions on the hands sustained while gardening without gloves. After conservative management with a trial of non-sedating antihistamines and 2 courses of antibiotics (clarithromycin and moxifloxacin), the swelling persisted. As such, 150 units of Hylenex® were injected into the left dorsal hand, with repeat injection two days later. A 2-week prednisone taper starting at 40 mg was also given, resulting in significant improvement (Figure 3B).

## DISCUSSION

DIRs are an uncommon complication that occurs following soft tissue augmentation, including with HA dermal fillers.<sup>1</sup> They are unpredictable and may occur in both previously injected and first-time patients.<sup>2</sup> Although definitions vary, an expert panel<sup>3</sup> agreed that DIRs occur at least two weeks following filler administration, after a quiescent state prior to flare-up. Reactions may manifest as erythema, edema (usually solid, non-pitting), nodules, and/or induration. Although DIRs are categorized as one entity, they likely represent a spectrum with infectious and immune-related pathogenesis being most likely.

Different triggers have been associated with DIRs, many of which are linked to injector-related circumstances such as inadequate skin preparation, large filler volume, repeated treatments, intramuscular implantation, and improper technique.<sup>4,5</sup> However, product-related factors have also been implicated. Specifically, HA fillers, composed of sodium hyaluronate cross-linked with 1,4-butanediol diglycidyl ether, vary in their cross-linking process depending on the manufacturer. It is hypothesized that larger molecules that are no longer recognized by the body as HA may lead to foreign-body reactions. Additionally, impurities or bacterial contamination from the cross-linking process may precipitate DIRs.<sup>2</sup>

The specific immunologic mechanisms by which DIRs occur are not entirely understood. One hypothesis suggests a cell-mediated hypersensitivity reaction, whereby low-molecular-weight HAs and by-products become immunogenic, leading to a delayed-type hypersensitivity reaction and downstream cytokine cascade. Belezny et al<sup>4</sup> suggest that these pro-inflammatory

HA fragments may be released following triggers that lead to a systemic inflammatory response. Infectious, biofilm-related, and other foreign-body reactions are also considered etiologic possibilities.

Regardless of the mechanisms, various triggers of DIRs have been described, including infections (especially respiratory), immunologic phenomena (vaccines), and trauma (dental procedures).<sup>3,6,7</sup> To the authors' knowledge, no case of filler reactivation has been reported following motor vehicle accidents, gardening, or contact dermatitis after laser resurfacing.

The management of DIRs depends on various factors, including the severity of clinical manifestations. For example, diffuse erythema and non-pitting edema at filler sites would be managed differently than small, isolated nodules. An expert panel describes a stepwise approach<sup>3</sup> to managing DIRs, which includes watchful waiting, systemic corticosteroids, incision and drainage of abscesses, antimicrobials, hyaluronidase, as well as intralesional corticosteroids and/or 5-FU.

## CONCLUSION

The popularity of HA fillers is increasing, and as such, injectors need to be equipped to manage and counsel patients on complications such as DIRs. We presented three cases of patients who developed DIRs to HA fillers following different triggers: motor vehicle accident, gardening without gloves, and suspected contact dermatitis following laser resurfacing. Overall, the exact mechanism by which DIRs occur is not fully clear. However, various systemic inflammatory insults, physiologic stressors, or skin barrier compromise may trigger these reactions. Given that these may not always be preventable, it is important for patients to understand the risk of DIRs occurring, albeit small.

## DISCLOSURES

The authors have no conflicts of interest to declare.

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