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CASE REPORT



An anaphylactic reaction after simultaneous injection of hyaluronic acid fillers and human collagen

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ABSTRACT

Anaphylaxis is rare following the injection of hyaluronic acid fillers or human collagen for esthetic improvement of the face. We report a case occurring in a 63-year-old woman treated simultaneously with both. Symptoms included full-body urticaria and gastrointestinal symptoms that declined within a few hours, facial redness and swelling lasting a few days, and a nodule in the right tear trough that recurred over several months. Treatment with corticosteroids and antihistamine ultimately supported a complete recovery. Although rare, practitioners using injectables should be trained to manage anaphylactic events if they occur.

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KEYWORDS

Anaphylaxis; collagen; filler; hyaluronic acid

Introduction

The use of injectable dermal fillers is a popular esthetic procedure. In 2019, it was estimated that over 4 million such treatments were performed worldwide using hyaluronic acid (HA) fillers alone (1). Of these, around 125,000 were in Japan (1).

Key factors underlying this popularity include ease of use, short patient downtime, and a low frequency of side effects. Indeed, adverse events are typically mild and localized to the injection site, such as bruising, swelling, and erythema. In most cases, they resolve within a few days.

Instances of allergy to the injected materials – sometimes termed ‘inflammatory reactions’ – are rare, and there are few reports in the literature of anaphylactic reactions to filler products. However, such events are possible and here we report a case of anaphylaxis after simultaneous injection of HA and human collagen.

Case report

A 63-year-old woman presented requesting rejuvenation of her entire face with HA filler and human collagen injections (Figure 1a). The patient had undergone facelift surgery 2 years previously but had no experience of injectable treatments. She had no relevant medical history other than mild hayfever.

Patient preparation followed our usual protocol. Fifteen minutes before commencing treatment, an anesthetic cream was applied containing 9.6% lidocaine. In addition, 0.025% (w/v) benzalkonium chloride solution was used for skin preparation.

The products injected were: Vycross 20 mg/mL HA (VYC-20 L; Juvéderm® Voluma™, Allergan, Dublin, Ireland), Vycross 17.5 mg/mL HA (VYC-17.5 L; Juvederm® Volift™, Allergan), and human collagen (Humallagen, Cosmetic Medicine Enterprises Inc., Palm Harbor, FL, USA; available only in

Japan). All contained lidocaine. The HA fillers were widely injected into the zygomatic arch, subzygomatic depression, nasolabial folds, marionette lines, and deep medial cheek fat (Figure 1b). Human collagen was used only in the right-side tear trough.

Once treatment commenced, the patient immediately complained of severe pain at the injection sites and demonstrated minimal lacrimation. After HA and collagen injections had been completed on the right side, and treatment progressed to HA use in the left zygomatic arch and subzygomatic depression, she complained of abdominal colic and nausea. This was around 20 minutes after starting treatment. Externally, there were no signs of swelling or redness at the injection sites, with only slight redness around the eye fissure due to lacrimation. The patient wanted to complete the treatment, but the injector insisted on postponement to another day.

Before discharge, the patient was given a routine prescription of prednisolone (PSL) 20 mg to reduce any inflammatory reaction and swelling.

After returning home (~1–2 hours post-treatment), she developed extensive facial redness and swelling, mainly in the treated areas but also in her forehead and upper and lower eyelids (bilaterally) (Figure 1c). In addition, she had urticaria all over her body (Figure 1d), and the gastrointestinal (GI) symptoms of abdominal colic and vomiting continued to worsen.

Around 4 hours post-treatment, the symptoms began to subside without medication. At this point (which was late at night), the injector read an e-mail from the patient, and although the peak of symptoms had already passed, she was instructed to take PSL 20 mg for the prevention and relief of delayed or biphasic anaphylaxis.

By the following day, the general urticaria and GI symptoms had completely subsided, and only redness and swelling of the upper and lower eyelids remained – primarily on the right side

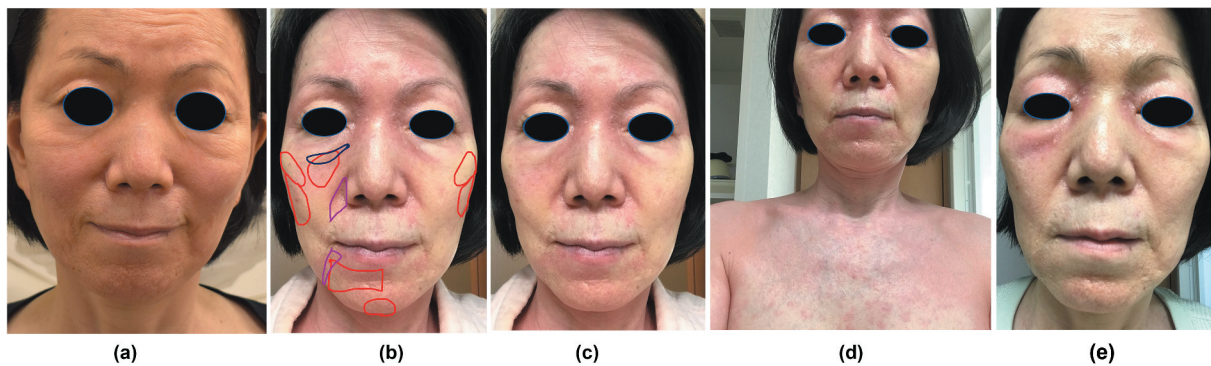


Figure 1. An anaphylactic reaction after simultaneous injection of hyaluronic acid fillers and human collagen. The figure shows a 63-year-old female before treatment (A) and the areas injected (B; red = Juvéderm Voluma; purple = Juvéderm Volift; blue = Humallagen). Around 1–2 hours after treatment, the patient showed erythema and swelling on the face (C; the mid-to-lower area of the left side of the face, where no treatment was given, was less erythematous) and urticaria over her entire body (D). By 14 hours post-treatment (E), symptoms had subsided except for swelling and redness of the upper and lower eyelids, primarily on the right side. The photographs in parts B–E were taken by the patient herself.

(Figure 1e). These residual effects were considered to be a shift to delayed symptoms of acute inflammatory reaction, and hence oral PSL 20 mg/day and epinastine hydrochloride 10 mg/day were started.

After about 1 week, a nodule was observed in the right tear-trough area, and triamcinolone acetonide 0.5 mg (diluted by 50% with saline solution) was injected locally several times over the following weeks. Hyaluronidase 30 U was also injected once into the same area, but was ineffective. After the nodule became smaller, mild swelling of the right lower eyelid – appearing at the same time as urticaria of the lower limbs – occurred once or twice per week for a duration of several months. This became mild after about 3 months and disappeared after 5 months.

The onset of this patient's adverse reaction was during the COVID-19 pandemic, and an immunoglobulin G (IgG) antibody test and other blood tests were only performed 2 months after the initial treatment. The IgG antibody test was negative, and there were no other allergy-related findings except a slightly elevated antibody titer to pollen and a high immunoglobulin E level of 6030 IU/mL.

The patient received two doses of the Pfizer COVID-19 vaccine at 3-week intervals starting around 2.5 months after the initial procedure. Swelling of the lower eyelid flared up temporarily 2 weeks later but resolved in 3 days with oral epinastine hydrochloride 10 mg/day.

A summary of the time course of symptoms and treatments is provided in Figure 2.

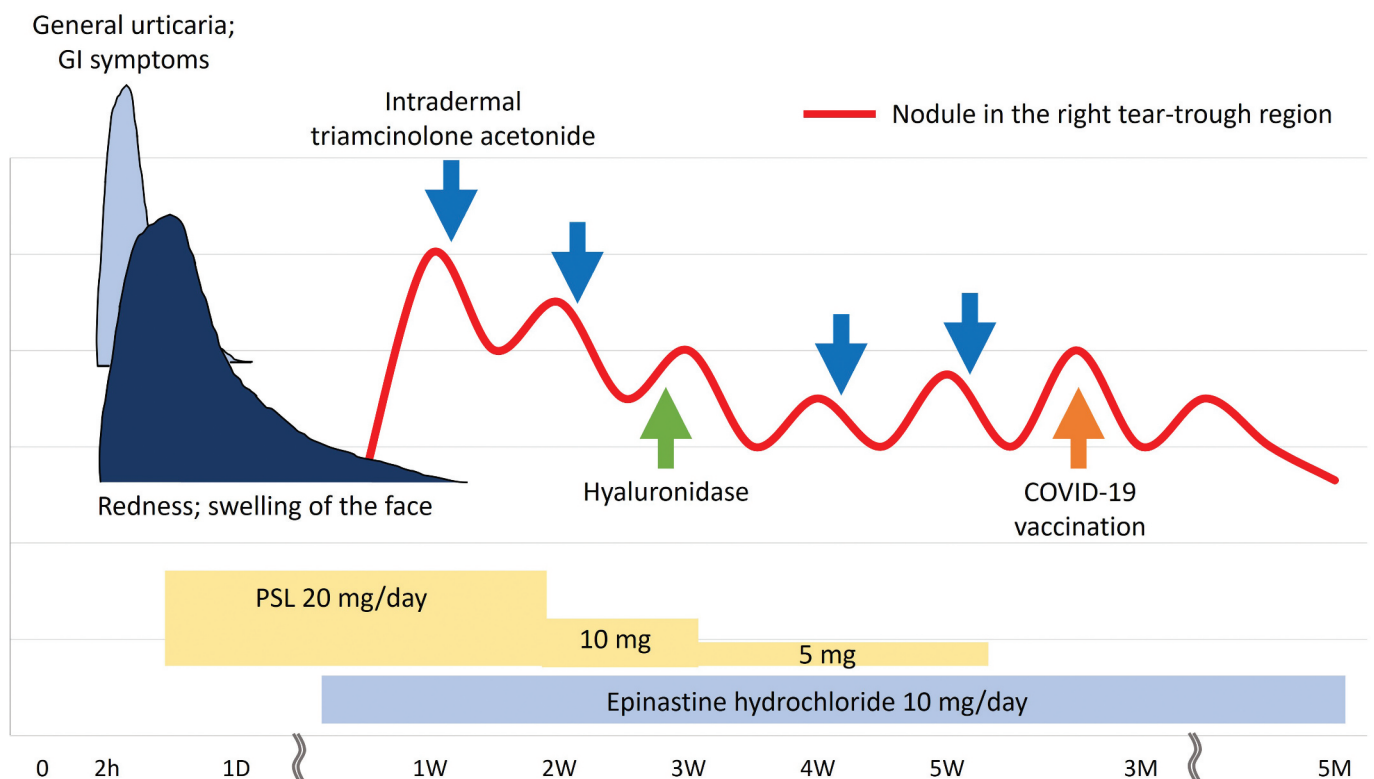


Figure 2. Approximate time course of symptoms and treatments. D, day; GI, gastrointestinal; h, hour; m, month; PSL, prednisolone; w, week.

Discussion

To the best of our knowledge, there are no previous published reports of anaphylaxis due to an injectable HA or human collagen treatment – although there is an account from 1996 of such a case following use of a *topical* bovine collagen preparation (2).

Based on the criteria defined by the World Health Organization (3), the patient in the present report experienced anaphylaxis because two key conditions were met: (i) skin and mucosal symptoms such as generalized rash, itching, flushing, and edema; and (ii) persistent GI symptoms (abdominal colic, vomiting), which occurred within a few minutes to a few hours after exposure to the potential allergen. GI symptoms in anaphylaxis are an effect of histamine-induced smooth muscle contraction, and if they emerge before other symptoms, care should be taken because the diagnosis of anaphylaxis may be delayed. Epinephrine was originally the first choice of treatment, but the symptoms had already passed their peak by the time they were fully reported, and hence the physician decided to treat the patient with steroids only.

The possible causes of anaphylaxis in this case include HA, human collagen, **other filler components (e.g. the 1,4-butanediol diglycidyl ether crosslinker or physiologic buffer solution within the HA products)**, anesthetic preparations, and needle stimulation. The patient had experienced no reaction to the anesthesia used during her previous facelift surgery and multiple dental treatments, or to triamcinolone acetonide and hyaluronidase treatments after the onset of anaphylaxis. Hence, it is unlikely to have been caused by anesthetics or needle stimulation, and the more probable cause was either HA or human collagen. However, it is difficult to differentiate between these two possibilities. **We considered performing gold-standard allergic analyses (patch tests, skin prick tests, etc (4)) to determine the cause, but decided against this at the time, owing to concerns the tests themselves could cause another anaphylaxis.**

The symptoms were more severe in the right lower eyelid, which was injected with HA into the suborbicularis oculi fat and pre-maxillary space, and with human collagen into the tear trough, in very close proximity to each other. The patient's photograph of herself taken at the time of onset of symptoms (Figure 1c) shows that there was almost no redness in the middle and lower area of the left side of her face, where no HA was injected. This suggests that HA might have been the cause of the anaphylaxis. However, given that the most severe symptoms and the residual nodule formation occurred in the right lower eyelid – treated with human collagen – the possibility that this caused the anaphylaxis cannot be ruled out.

It is noteworthy that the lower eyelid swelling flared up following injection of a COVID-19 vaccine. There have been other reports of (rare) swelling events following filler treatment in vaccinated patients (5,6), and this may require further assessment.

Conclusions

We report a rare case of anaphylaxis following the simultaneous injection of HA and human collagen products for esthetic treatment of the face. Despite the infrequency of these events, medical professionals who administer injectables must be trained and prepared to properly handle an anaphylactic reaction.

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Disclosure statement

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