

Angioedema after ovine hyaluronidase injection for treating hyaluronic acid overcorrection

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Summary

Background Hyaluronic acid injections are becoming popular in aesthetic dermatology, and, sometimes, misplacements and very rarely adverse events have been reported. Hyaluronidase, an enzyme that hydrolyzes hyaluronic acid, is used to treat overcorrection or granulomatous reactions. Allergic reactions are well known except for how frequent they occur.

Objective This paper aims to confirm the efficacy of hyaluronidase injections to dissolve hyaluronic acid, but insists on the risk of hypersensitivity with animal-derived products.

Methods A case of angioedema due to ovine hyaluronidase is reported, and treatment is discussed.

Conclusion Hyaluronidase is highly effective, but skin test must be done before injection to avoid risk of angioedema and/or Quincke's edema.

Keywords: angioedema, hyaluronic acid, hyaluronidase, prick test

Introduction

Aesthetic dermatology is growing up fast, and hyaluronic acid (HA) injections are more and more used. HA is a very safe product produced principally by bacterial fermentation; it is actually the "gold standard" as a filler agent.¹ No skin testing is required even if rare adverse reactions have been reported.^{2,3}

Recently, hyaluronidase therapy has been proposed to remove granulomatous reactions or unsightly lumps and masses protruding under the skin.^{3–5} Hyaluronidase is usually derived from bovine, ovine, or snake venom and is potentially allergenic. Before injection, it is safer to test the patient first even if allergic reactions are not well described in literature.

In this paper, we report a case of an immediate allergic reaction to an ovine-derived product.

Case report

A 35-year-old woman has been regularly injected with HA without experiencing any trouble. A few days after HA (Surgiderm® 24 XP, Allergan-Corneal, USA) lip augmentation, she found that her upper lip looked lumpy (Fig. 1); thus, we decided to treat her with hyaluronidase injection.

As usual, we proposed a skin test, and we asked her to come back 3 days later, for eliminating a potential risk of allergic reaction.⁵ As the patient was leaving for vacation, she insisted on doing hyaluronidase injection immediately. After informed consent was obtained, and the patient photographed, we accepted to treat her.

A 4% ovine-derived hyaluronidase powder (Desinfiltral®, Aesthetic Dermal UK), 1 vial (1 500 U), was diluted with 4 mL of physiologic saline and 0.3 mL (112.5 U) was then injected into the upper lip. No anesthesia was used. The patient left our office. Ten minutes later, we received a call from her, telling us that she was "swelling." She came back to the office with an angioedema of the face (Fig. 2).

Edema started around mouth and evolved all over the upper face within 15 min. One vial of 4 mg of betamethasone

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Figure 1 "Slight lumpy" aspect of the upper lip.



Figure 2 Angioedema of the face.

was injected and patient rested for 2 h. No edema of the tongue nor breathing trouble were detected.

After 2 h, during which time the edema rapidly subsided, the patient left with prednisolone 40 mg b.i.d. for 3 days. The next day, the patient called the office to confirm her good state except for a small persisting swelling around her eyes.

A few days later, she came to the office with a natural look and a reduction of the volume of her upper lip (Fig. 3). We corrected the asymmetry of the lower lip, by a new HA injection into her upper lip, and she went out happy.

Discussion

Hyaluronidase, a soluble protein, is an enzyme that hydrolyzes complex hyaluronan glycosaminoglycan polysaccharides. Hyaluronidase hydrolyzes HA by splitting



Figure 3 The upper lip has returned "natural."

the glucosaminidic bond between C1 of the glucosamine moiety and C4 of glucuronic acid.

Most available products are bovine, ovine, or venom cobra derived. Efficacy on HA dissolution is high, but there is a potential risk of allergic reactions due to animal-derived products. Some delayed or immediate hypersensitivity have been reported, but details concerning these reactions are very scant.

Some articles report a 0.1% of allergic risk, but most are from ophthalmic surgery departments, and it is probable that the skin is more prone to allergic reactions than the eyes.⁶ Three cases of immediate hypersensitivity with angioedema after cataract surgery have been reported.⁷ In these cases, prick tests were positive. Muller *et al.* reported a case of angioedema after dental anesthesia with hyaluronidase, with specific serum immunoglobulin E antibodies detected by radio-allergo-sorbent test (RAST).⁸ Furthermore, Szépfalusi *et al.* reported five pediatric cases of immunoglobulin E-mediated reactions in an oncologic center.⁹ Delayed periorbital inflammation has been reported to occur 24 to 72 h after cataract surgery. The exact percentage of hypersensitivity to hyaluronidase is not perfectly known. Overall, raw hyaluronidases are not similar and do not come from the same origin.

In the present study, the patient revealed a history of atopic dermatitis and asthma during an inquiry. However, she is not allergic to wasp or yellow jacket bites.

Before testing and/or treating a patient with hyaluronidase, inquiry for allergic background and hypersensitivity to insect bites is suitable.¹⁰ Some medications (furosemide, benzodiazepines, phenytoin) are incompatible with hyaluronidase, which can decrease their effectiveness. It is important to not inject hyaluronidase in an infected tissue, to avoid spreading of infection.

In the United States, Wydase® (ESI dedesle Generics, PA, USA) (a bovine hyaluronidase) was used for a long time, but it is no longer manufactured. Amphadase® (Amphastar, CA, USA) (a bovine testicular hyaluronidase) is launched in 150 U/mL vials: its manufacturer recommends preliminary skin test (intradermally at 0.02 mL = 3 U). A positive reaction consists of a wheal within 5 to 20 min. According to the company, there are less than 0.1% of urticaria/angioedema reactions; anaphylactic reactions are very rare.

Vitraxe® (ISTA, CA, USA) (an ovine testicular hyaluronidase) is launched in 200 U/mL vials. Skin test needs to be performed before injections.

Spreadase® (CHANDRA BHAGAT Pharma, India) (an ovine hyaluronidase), not approved by the Food and Drug Administration, is launched in 1500 U powder vials.

The exact protein load of each of these hyaluronidases is not reported, and no study has evaluated the skin allergic risk.

In the future, we hope to use the first recombinant human hyaluronidase (Hylenex®, Halozyme Therapeutics, San Diego, CA). The purity of this hyaluronidase is 100-fold higher than the current animal-derived hyaluronidase. In the literature, some articles report the action of Hylenex for hypodermoclysis without any allergic reaction.¹¹

The skin is probably more prone to hypersensitivity than the eyes, and we confirm the importance of skin testing before injection. We consider that risk is due to immediate hypersensitivity; thus, we recommend performing prick tests (Stallerpoint®, Stallergenes SA-France) before hyaluronidase treatment unless in an emergency situation.⁴ Prick tests are done with hyaluronidase, histamine, and saline (control tests). Reactions are read after 15 min and 30 min and controlled by the patient until 6 h. The test is positive if wheal and flare are 3 mm more than that of the controls. Anaphylactic reaction can occur, especially after having IDR performed, hence the importance of prick tests.

It is safer to keep the tested patient for 30 min in the office to detect any signs of Quincke's edema and anaphylactic reaction.

Management of this acute urticaria must be well known. Corticosteroids are administered by intramuscular injection (betamethasone, methylprednisolone) with or without antihistamines. In case of mucous involvement and systemic signs (tachycardia, breathing distress, hypotension, etc.), epinephrine injection is added (oral spray, oral taking, subcutaneous injection) to avoid anaphylactic shock.

After resolving the acute crisis, systemic prednisolone (40 mg to 60 mg once a day) for 3 days is useful.

Conclusion

This case report confirms the high efficacy of hyaluronidase on HA overcorrection. Even if rate of type I hypersensitivity reactions is not well known and probably very low, we believe that it is safer to perform prick tests before injecting animal-derived products.

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