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ABSTRACT

Hyaluronic acid(HA) is biocompatible, easy to use and reversible. HA fillers are considered to be safe, although some complications can occur. At this time, hyaluronidase is used off-label for correction. A 41-year-old woman presented to our clinic for focal erythematous plaque on hyaluronidase injection site. She got the injection for correction of HA filler excess. The skin lesion continued for 7 days. Histopathologic findings were nonspecific. On intradermal skin test, allergic reaction to hyaluronidase were confirmed. Adverse effects of this hyaluronidase are uncommon with local injection site reactions most frequently reported. Allergy to hyaluronidase should be included in the differential diagnosis when focal erythema and swelling occur after hyaluronidase injection.

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ABSTRACT

Hyaluronic acid(HA) is biocompatible, easy to use and reversible. HA fillers are considered to be safe, although some complications can occur. At this time, hyaluronidase is used off-label for correction. A 41-year-old woman presented to our clinic for focal erythematous plaque on hyaluronidase injection site. She got the injection for correction of HA filler excess. The skin lesion continued for 7 days. Histopathologic findings were nonspecific. On intradermal skin test, allergic reaction to hyaluronidase were confirmed. Adverse effects of this hyaluronidase are uncommon with local injection site reactions most frequently reported. Allergy to hyaluronidase should be included in the differential diagnosis when focal erythema and swelling occur after hyaluronidase injection.

Key words: Allergy, Hyaluronic acid (HA), Hyaluronidsae

INTRODUCTION

Soft tissue augmentations become more popular because a demand in noninvasive rejuvenation is increased recently. Among them, hyaluronic acid (HA) fillers are most commonly used because HA is less immunogenic, natural polysaccharide and hygroscopic¹. Although HA fillers are considered to be safe, some trivial to severe complications can occur (e.g., excessive use of product, too-superficial injection, granulomatous foreign-body reaction, and injection necrosis). The management of these undesirable events with hyaluronidase is gaining popularity because of its safety, efficacy, and ease of use. However, hyaluronidase has been shown to be a potential cause of allergic responses. While it is a known allergen, there are few reports of allergic reactions in dermatology. The authors report a case of allergic reaction to hyaluronidase in correction of HA filler.

CASE REPORT

A 41-year-old Korean woman was present with tingling focal erythematous plaque on right nasolabial fold. (Fig. 1) She had got HA filler injections for both nasolabial folds at another hospital. However, 2 months later, she noted that the right side of her nasolabial fold was larger than her left, so she got a hyaluronidase injection for correction of her right nasolabial fold. 2 hours

later, erythematous edema was present on her injection site. So she took an antibiotic therapy for 7days, but it wasn't improved. On past history, she had no history of preceding cutaneous disease or localized contact of something. A biopsy specimen taken from a erythematous lesion on her right nasolabial fold showed mild spongiosis in the epidermis with perivascular lymphocytic infiltration in the dermis by Hematoxylin-Eosin stain(Fig.2).

Patch testing was carried out to the 24 kinds of quantified allergens obtained from T.R.U.E test®(SmartPractice; Denmark ApS, Hillerød, Denmark) and HA(Hyruan®; LG chemistry, Korea). Hyaluronidase was not available for patch testing. Patches were applied to the upper back and left on for 48 hours. Reactions were recorded 30 min after patch removal at 48 hours and at 96 hours according to the International Contact Dermatitis Research Guidelines. Patch tests were negative except for nickel. Additionally, skin prick test and intradermal test were carried out. The agents tested were HA (Hyruan®; LG chemistry, Korea) and hyaluronidase 1500IU (H-lase®; Kuhnle, Korea). Normal saline was used as negative control. Histamine 0.1% was the positive control by the skin prick method only. Intradermal test with hyaluronic acid on left arm was negative, but hyaluronidase(15U) on right arm produced positive wheal and flare in 30 minutes. 2 days later, positive

reaction at test site was even more exacerbated (Fig. 3).

Based on those findings, she was diagnosed with allergic reaction to hyaluronidase. Since then, she was treated with systemic corticosteroid, antihistamine and topical steroid cream and was improved in 4 days.

DISCUSSION

Hyaluronidase is a naturally occurring enzyme that degrades hyaluronic acid, one of the four main glycosaminoglycans that constitute the dermal extracellular matrix and can easily manage unwanted events of HA filler such as overcorrection, misplacement and skin necrosis¹. However, because most medical hyaluronidases are made of bovine, ovine, and caprine testes and these proteins can provoke a hypersensitivity, a preliminary skin test of hyaluronidase(3U) is officially recommended². However, when we use hyaluronidase to correct HA filler side effect, it is often very difficult to perform skin test in dermatologic clinic for several causes.

Fortunately, adverse effects of Hyaluronidase are very uncommon and local injection site reactions are frequently reported. There are no report of anaphylactic reaction after subepidermal injections¹. Since Kempeneers et al reported first allergic reaction to hyaluronidase after retrobulbar anesthesia in 1992³, similar cases have been reported rarely and most cases were after

retrobulbar block in ophthalmologic surgery⁴. The onset of the allergic response is reportedly variable Immediate(within a few minutes), early(within a few hours), intermediate(within a few days) or late(within weeks). These findings suggest that both type I and type IV hypersensitivity are likely to contribute to this response⁴. The dosage of the drug is associated with the allergic reaction to hyaluronidase. With local reactions the dose administered ranged from 100 to 150 U. Patients with Systemic reaction received an intravenous dose ranging from 1,500 to 200,000U. Cumulative dose is not related to clinical manifestations⁵. Treatment with steroids and systemic antihistamines results in resolution of the signs and symptoms within a few days.

Most of patients with hyaluronidase allergy had a positive skin prick or intradermal test for type I hypersensitivity⁴. Our patient in intradermal test produced positive wheal and flare in 30minutes. Positive reaction at test site was even more exacerbated 2 days later. we first thought these extended reaction was caused by overabsorption of allergen because we used higher dose of hyaluronidase(15U) for skin test than recommended dose(3U).

Second thought is that type I and type IV(delayed cell mediated) hypersensitivity simultaneously might cause this reaction. Prolonged

intradermal reaction for 2 days can suggest type IV hypersensitivity.

The blood test, including white blood cell count, erythrocyte sedimentation rate, C-reactive protein, and procalcitonin level could be useful to make a differential diagnosis with an infection. Fever and systemic symptoms also mean an infection⁶. Local injection site reaction is that an erythema disappears within 24 hours and skin allergy tests is negative². High dose hyaluronidase can provoke responses similar to hypersensitivity such as non infectious swelling and inflammation. But on the former occasion, skin allergy tests are normal⁷.

As HA filler augmentations become more popular, some trivial to severe complications can occur. Hyaluronidase can easily manage these unwanted event, so the use of hyaluronidase will be more increased in dermatology. Although rare and mostly benign, when focal erythema and swelling occur after hyaluronidase injection, allergy to hyaluronidase should be included in the differential diagnosis. For this reason, we report a rare case of allergic reaction to hyaluronidase used after hyaluronic acid filler injection.

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Figure Legends

Fig.1 (A) focal erythematous edema on the nasolabial fold. (B) closer view.

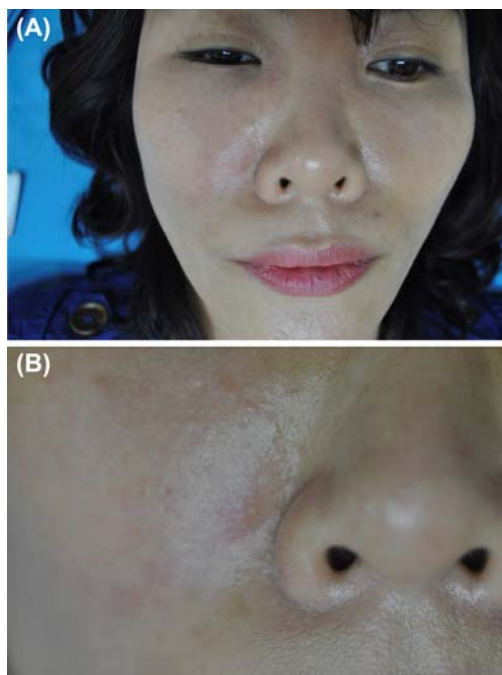


Fig.2 A biopsy specimen taken from a erythematous lesion on the nasolabial fold showed mild spongiosis in the epidermis with perivascular lymphocytic infiltration in the dermis(A&B). Periappendageal lymphohistiocytic infiltration was shown in deep dermis. There was no giant cell(C). Hematoxylin-Eosin stain. (A. H&E X40, B,C. H&E X200)

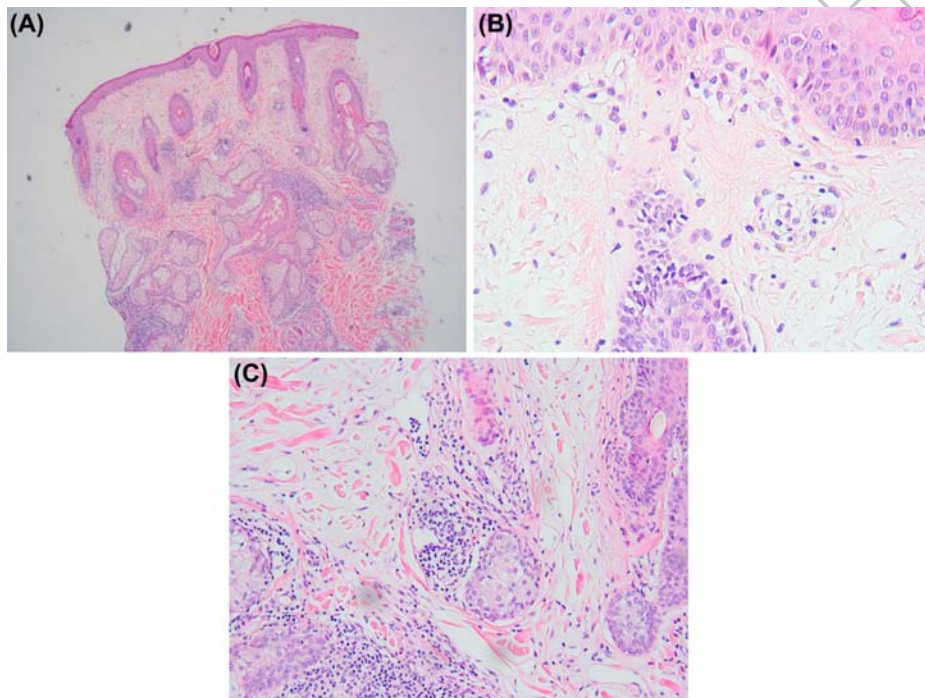


Fig.3 Skin testing by the skin prick and intradermal methods was carried out with hyaluronic acid and hyaluronidase. Intradermal testing with hyaluronic acid was negative(A), but hyaluronidase was positive in 30 min(B). 2 days later, positive reaction at test site was even more exacerbated(C).

