

Novartis, Lilly, Almirall, Leo-Pharma Payment honoraria for lectures and presentations; Pfizer, MSD, Abbvie, Janssen, Novartis, Lilly, Almirall, Leo-Pharma Support for attending meetings and/or travel; Abbvie, Janssen, Novartis, Lilly, Almirall, LeoPharma Participation on Advisory Board. Ramon M Pujol; none. Marta Ferran Farrés; Pfizer, MSD, Abbvie, Janssen, Novartis, Lilly, Almirall, Leo-Pharma, Payment or honoraria for lectures and presentations; Pfizer, MSD, Abbvie, Janssen, Novartis, Lilly, Almirall, Leo-Pharma, Support for attending meetings and/or travel; Abbvie, Janssen, Novartis, Lilly, Almirall, LeoPharma Participation on Advisory Board.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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DOI: 10.1111/jdv.18131

Delayed hypersensitivity of hyaluronidase: a case report

Dear Editor,

With the increasing popularity of dermatologic surgery, hyaluronic acid (HA) dermal fillers have become the dominant material for use in recent cosmetic procedures.^{1,2} HA is a glycosaminoglycan, one of the body's own substances in the form of a linear polysaccharide consisting of glucuronic acid and N-acetyl-glucosamine found in the extracellular matrix of connective tissue, hyaline cartilage.^{1,2} It draws water into the skin, giving it volume while binding collagen and elastin fibres into a supportive matrix.³ Increased usage of HA fillers led hyaluronidase to become an essential drug to reverse misinjection of HA filler.

Although the use of hyaluronidase has increased significantly, practitioners have few opportunities to study hyaluronidase. Moreover, previous studies covering hyaluronidase allergy were mostly limited to the field of ophthalmic surgery. Herein, we present two cases of allergic reaction to hyaluronidase, respectively.

A 23-year-old woman presented excoriated skin lesion with pruritus for 1 month. She had experienced burn on the both upper extremities by boiled water 2 years ago and had scar contracture (Fig. 1a). This area was treated by several times of hyaluronidase (Hirax) intra-lesional injection (1500 IU) with laser therapy for a year. Suddenly, she had itching sensation localized in injection area 1 month ago. Routine laboratory findings were within normal ranges. She had negative result in the patch test. She was treated with antihistamine under diagnosis of irritant contact dermatitis.

Next, a 42-year-old woman had erythematous skin eruptions with heating sensation on both cheeks for 3 months. She had been treated six times of dermal fillers (Style 4) and hyaluronidase (Hyalrheuma, Hrase) on her face alternately for 2 years. She had potassium and thiuram contact allergy in the patch test. The physical examination revealed erythematous patches on her both cheeks (Fig. 1b). Routine laboratory findings showed no abnormal findings. She was treated with doxycycline under diagnosis of rosacea.

Since both patients had a history of hyaluronidase injection, we consider hyaluronidase allergy. Skin prick tests of hyaluronidase were negative; however, intradermal tests using hyaluronidase were performed and showed immediate reactions, erythema and weal in both patients (Fig. 2). In addition, intradermal test using dermal filler was conducted in second patient and showed immediate allergic reaction. Based on the specific history of hyaluronidase injection and positive result of intradermal test with hyaluronidase, the final diagnosis was hyaluronidase allergy.

The more cross-linking, the more difficult it is for hyaluronidase to access its binding sites inside the HA filler. Rarely, an



Figure 1 (a) Scar contracture with excoriation on her both upper extremities. (b) The physical examination revealed erythematous patches on her both cheeks.

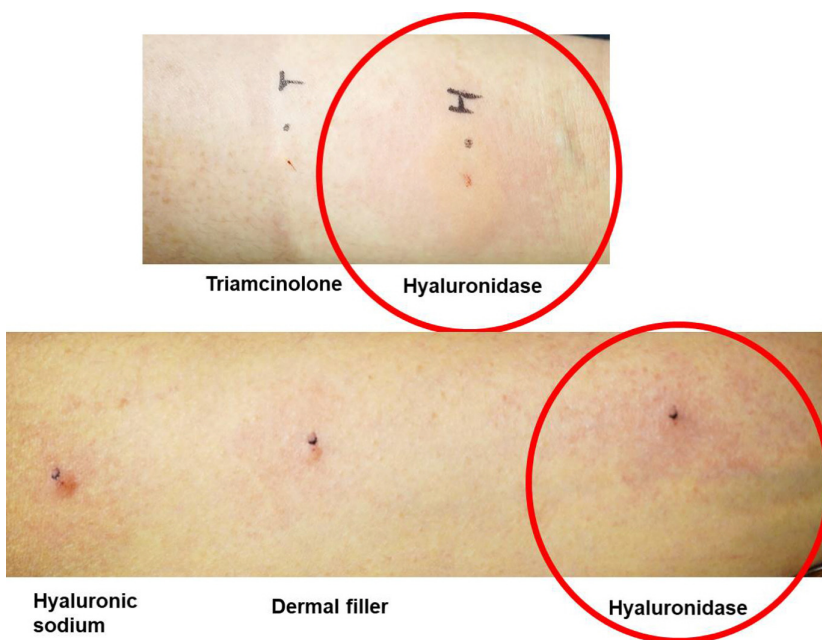


Figure 2 Intradermal tests using hyaluronidase were performed and showed immediate reactions such as erythema and weal in both patients.

allergic reaction to hyaluronidase may occur. The incidence of allergic reactions is reported to be 0.05%–0.69%, and urticaria and angioedema have also been reported to occur at a low frequency (less than 0.1%).^{5,6} And also in a study by Yocum *et al.*, 100 volunteers injected intradermally with human recombinant hyaluronidase did not develop any allergic reactions.

However, depending on the origin of hyaluronidase, injection of hyaluronidase should be avoided because cross-reactions may

occur in patients who are allergic to bovine collagen and bee stings.⁷

Delayed hypersensitivity caused by hyaluronidase can occur even after 24 h; in such cases, a skin test will not produce a positive reaction within 20 min, resulting in a negative diagnosis.^{8,9,10} In such cases, systemic steroids, antihistamines and topical corticosteroid are helpful, and both patients were treated with these treatments. In other case reports, most of these

patients were treated with oral or intravenous steroids, oral antihistamines and antibiotics in previous reports.⁴

In conclusion, because the prevalence of hyaluronidase allergy is rare, there is no consensus on clear treatment methods. As the use of hyaluronidase becomes more frequent, it is necessary to clearly recognize the side-effects and treatments of hyaluronidase allergy.

Acknowledgements

The patients in this manuscript have given written informed consent to the publication of their case details.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding sources

This study was supported by grants from the National Research Foundation of Korea (NRF).

Data availability statement

Data openly available in a public repository that issues datasets with DOIs

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DOI: 10.1111/jdv.18133

Palmoplantar keratoderma with deafness due to *GJB2* mutation can develop ichthyosiform symptoms: a case report

Editor

Gap junction protein beta-2 (*GJB2*), also known as connexin-26, is widely expressed in the body, especially in the epidermis, cochlea and cornea, and it plays a crucial role in gap junction formation and function.^{1,2} Mutations in *GJB2* cause both autosomal-recessive and dominant non-syndromic hearing impairment (HI) and are responsible for autosomal-dominant syndromic HI with various skin manifestations.^{1–4} There are some types of *GJB2*-related skin diseases, and they have a certain degree of genotype–phenotype correlation.^{1–4} Of these disorders, palmoplantar keratoderma (PPK) with deafness shows diffuse palmoplantar hyperkeratosis and prelingual or postlingual HI.^{1–6} Here, we report siblings with PPK with deafness who also show ichthyosiform symptoms that have not been observed in previous cases.

An 8-year-old brother and a 9-year-old sister were referred to our department with PPK and sensorineural HI, present since childhood. Although their parents were not consanguineous, both were also affected by severe HI (Fig. 1a). Physical examination of the siblings revealed mild but diffuse hyperkeratosis on the palms and soles (Fig. 1b,c). These lesions showed transgrediens and extended to the dorsal surfaces of the hands and feet, the ankles, the Achilles tendon areas, and the knees, which were more obvious in individual III-2 (Fig. 1d-f). Notably, they both had dry skin all over their bodies, with partial eczematous lesions. Moreover, leaf-like scales and keratosis pilaris on the lower legs and back were observed in individual III-2 (Fig. 1g,h). These symptoms showed exacerbation, especially in winter, but they had no signs of atopic dermatitis and allergic predisposition. Their father had palmoplantar hyperkeratosis, but no apparent dry skin (Fig. 1i). The histology of a lesion on the left foot of individual III-1 showed compact hyperkeratosis and a slightly thickened stratum granulosum without spongiotic changes (Fig. 2a,b). Based on the clinicopathological findings, PPK with deafness was highly suspected. *GJB2* and *MT-TS1* are important for PPK with deafness, but the former was more likely to be causative in this family from the mode of inheritance. Mutation analysis of *GJB2* (NM_004004.6) revealed the heterozygous missense mutation c.223C>T (p.R75W) in individuals II-2, III-1 and III-2 (Fig. 2c). It was not harboured by individual II-5, although a mutation in *MT-RNR1* (NC_012920.1, m.1555A>G), which is often responsible for non-syndromic HI, was identified. As this mitochondrial mutation is always inherited maternally, the siblings must