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CASE REPORT

Combination of Hyaluronic Acid and Polynucleotides Injection for the Treatment of Cheilitis Simplex

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Abstract: Cheilitis simplex is a prevalent form of cheilitis that is characterized by the presence of cracked lips, fissures, or desquamation, due to various etiologies. Utilization of "boosters" as a treatment for chapped lips has not been extensively researched. This case report aimed to describe the efficacy of lip booster injection comprising active ingredients of 1% hyaluronic acid (HA) and 1% polynucleotides (PN), with 0.3% lidocaine as anesthetic agent. A 30-year-old female patient presented with a chief complaint of dry and chapped lips that occasionally bleed. This condition had recently deteriorated, and the application of topical treatment had not yielded substantial improvement, which led to a state of distress for the patient. She was diagnosed with cheilitis simplex and was subsequently treated with a single subdermal injection of a combination of 1% HA, 1% PN, and 0.3% lidocaine. Lip hydration was increased gradually, as measured by tewameter, with peak rate of hydration (26.218 g/m^2/h) occurred two weeks after injection, and subsequently decreased gradually until six weeks after injection (29.926 g/m^2/h); however, the rate of hydration remained higher than the baseline value (34.386 g/m^2/h). Additionally, the lips exhibited an increase in brightness and a shift in pigmentation toward a rosier hue, as substantiated by spectrophotometric analysis. The mechanism of HA and PN include providing hydration and stimulating dermal fibroblast activity. However, PN may also exert an additional effect of improving lip pigmentation by reducing melanin and increasing hemoglobin levels. In conclusion, the lip booster injection, comprising 1% PN, 1% non-cross-linked HA, and 0.3% lidocaine, is an efficacious and practical treatment option for cheilitis simplex. This treatment option offers the additional benefits of being pain-free and enhancing lip pigmentation. Further studies are required to confirm these findings.

Keywords: cheilitis simplex, dry and chapped lips, hyaluronic acid, lip booster, polynucleotide

Introduction

The lips represent one of the most appealing characteristics of the human face, exerting a substantial influence on our perceptions of an individual's health and aesthetics.[1,2] They differ from the facial skin in several ways; notably, the lips have a weaker barrier function owing to the thin stratum corneum, which has only three to five layers, and incomplete keratinization in some areas.[1,3,4] In addition, there is a very low number of free sebaceous glands and no sweat glands to provide moisture.[3,4] These factors, in combination with constant exposure to environmental factors, render the lips more susceptible to dryness and peeling.[3–5]

Chapped lips, also known as cheilitis simplex, common cheilitis, or cheilitis sicca, is an inflammatory condition of the lips which is characterized by the presence of cracked lips, fissures, or desquamation, typically manifesting in the lower lip region.[6,7] It is one of the most prevalent subtypes of cheilitis, with a multifactorial etiology that includes, but is not limited to, irritation due to lip licking behavior, incessant biting of the lips (cheilophagia), and exposure to dry and/or windy climates.[6] The treatment typically includes the recommendation of measures to address environmental or behavioral factors that contribute to its development, the application petroleum jelly or lip balms and, in certain cases,

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the addition of topical low-potency corticosteroids.[7] However, there has been an increased demand for innovative therapeutic interventions that facilitate hydration from within the dermis rather than merely being topically applied.[1]

The term "skin booster" refers to injectable treatments composed of ingredients that are administered directly into the skin with the aim of improving its overall condition.[8,9] Nevertheless, a more precise term for the procedure of injecting a skin booster into the lips specifically to enhance the overall condition of the lips without altering their volume may thus be "lip booster".[10–12] A number of studies have previously investigated the utilization of lip booster comprising various active ingredients.[1,10–13] However, to the best of our knowledge, no studies have yet explored the combination of non-cross-linked hyaluronic acid and polynucleotide for the treatment of cheilitis simplex. The injection of non-cross-linked hyaluronic acid into the lips can provide hydration without adding volumization,[10,14] while the use of polynucleotide can yield subtle, natural rejuvenation by stimulating cell growth and promoting tissue repair.[15] This case report describes a case of cheilitis simplex that demonstrated improvement following a single subdermal injection of a formulation containing active ingredients of 1% hyaluronic acid and 1% polynucleotides, with 0.3% lidocaine as an anesthetic agent.

Case Presentation

A 30-year-old female patient presented to the Cosmetic Dermatology Clinic at Hasan Sadikin General Hospital, with a chief complaint of dry and chapped lips that occasionally bleed. This condition had been observed since the patient's childhood, but had recently worsened over the course of the past two weeks. The patient admitted to experiencing more frequent mouth breathing due to nasal congestion, particularly at nighttime, for the past month due to the recent drop in ambient temperature. She also reported a habit of unconscious lip licking when the lips felt dry and lip picking to remove scales on the lips, which occasionally resulted in bleeding and caused discomfort, especially during activities such as speaking and eating. The patient administered self-treatment by applying petroleum jelly as an occlusive agent to the lips overnight. This treatment resulted in a certain degree of relief the following morning. However, this effect was only transient, and the lips would begin to chap again after several hours.

The patient's medical history was unremarkable, with the exception of atopic dermatitis during childhood and recurrent allergic rhinitis, which had recurred intermittently until the present. She admitted that the use of lipstick and other cosmetic products on the lips caused more profound dryness of the lips. However, even upon cessation of the application of these products, complaints of chapped lips still persist. The patient also denied the use of any drug intake, including isotretinoin, and reported no history of sexual activity or contact dermatitis. Previous patch testing using the standard 15 allergen kit (PATCH•GEN, Swayasa Prakarsa, Yogyakarta, Indonesia) yielded no allergic reaction. The patient denied any history of other diseases that also manifest clinically as cheilitis, such as flaccid blisters and erosions, epidermolysis of skin and mucosal membranes, dry eyes and mouth, and others.

Upon physical examination, the patient was normoweight with body mass index of 18.52 kg/m^2. While no erosion was present, epithelial desquamation was observed and manifested as scales and visible single cracks, particularly on the lower lip. The severity of the patient's lip dryness was clinically evaluated using the photonumeric lip dryness grading scale (LDGS), which is based on the presence of lip roughness, scales, cracks, and fissures.[16] The evaluation resulted in a score of four out of eight, indicating the presence of moderate roughness, coarse scaling, and slight cracking. Initial transepidermal water loss (TEWL) was measured at 34.386 g/m^2/h using tewameter (Cutometer dual MPA 580, Courage + Khazaka electronic GmbH, Köln, Germany) while lip color measurement was performed using a spectrophotometer (Spectrophotometer CM-700d, Konica Minolta, Tokyo, Japan) and expressed based on Commission Internationale de l'Éclairage (CIE) L*a*b* color space. Laboratory examination showed normal total IgE (18.5 IU/mL) and serum iron (63 µg/dL). A diagnosis of cheilitis simplex was made, and the patient consented to undergo an injection procedure to alleviate her symptoms.

Following the application of a topical anesthetic cream to the lips for a duration of 30 minutes, a total of 1-mL subdermal injection was administered, containing 1% polynucleotide (PN), 1% hyaluronic acid (HA), and 0.3% lidocaine (Rejuran HB plus®, PharmaResearch Products Co. Ltd., Seongnam-si, South Korea). This injection was administered in five points over the four quadrants of the lips, resulting in a total of 20 points for the entire lips (Figure 1A). The injection was administered using a 4 mm, 33G hypodermic needle, with the needle tip inserted from the periphery of the lips and directed towards the center of the lips. Despite the absence of pain during the injection (pain visual analog scale [VAS] 0

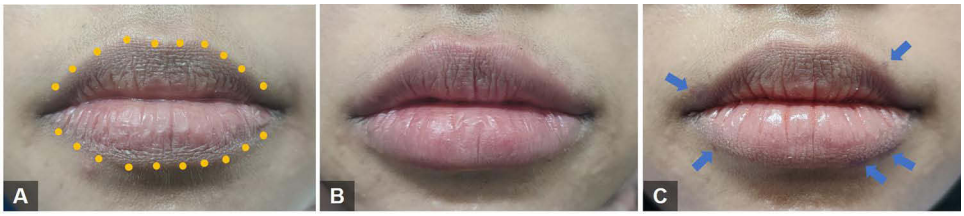

Figure 1 (**A**) Location of the subdermal 1% PN, 1% HA, and 0.3% lidocaine injections at the periphery of the lips (yellow dots). Injection site reaction consisted of: (**B**) swelling and throbbing pain within 30 minutes after the injection, and (**C**) bruising (blue arrows) that appeared at 1 day after the injection and started to fade at 3 days after the injection.

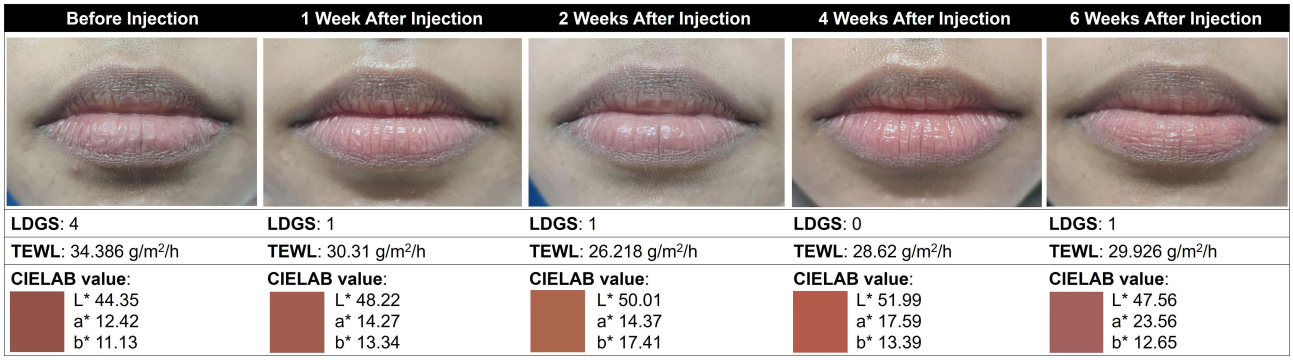

Figure 2 Clinical photographs, LDGS scores, TEWL, and CIELAB color values from baseline to 6 weeks after injection of 1% PN, 1% HA, and 0.3% lidocaine. Improvement of hydration and brightening of the lip colors can be noted up to 6 weeks after the injection. LDGS score 0, No dryness or chapping evident; 1–2, Slight but definite roughness and fine scaling; 3–4, Moderate roughness, coarse scaling, and slight cracking; 5–6, Marked roughness, coarse scaling, and obvious cracking; 7–8, Very marked roughness, coarse scaling, and cracked progressing to fissuring. TEWL values are expressed in g/m^2/h. Colored squares represent lip color derived from CIELAB measurements, with L* indicating lightness, a* indicating redness (green–red axis), and b* indicating yellow color (blue–yellow axis).
Abbreviations: LDGS, lip dehydration grading scale; TEWL, transepidermal water loss; CIELAB, Commission Internationale de l'Éclairage L*a*b* color space.

out of 10), the patient subsequently experienced moderate, throbbing pain (VAS 4 out of 10) for up to 30 minutes following the injection. This was accompanied by lip swelling (Figure 1B) that persisted for up to 36 hours and slight bruising in multiple areas (Figure 1C), which improved within 3 days post-injection.

The patient reported a marked improvement in hydration three days after the injection, noting that her lips were no longer chapped in the morning, despite not applying petroleum jelly overnight and continuing to breathe through her mouth due to a congested nose during sleep. The hydration exhibited a daily increase, reaching a peak at approximately two weeks after injection, as indicated by a TEWL of 26.218 g/m^2/h. Furthermore, she observed a decrease in the frequency of lip-licking and lip-picking behaviors, which she attributed to the hydrated sensation and the absence of scale on her lips after the treatment. The patient reported a decrease in hydrated sensation, which was concomitant with a reduction in TEWL of 28.62 g/m^2/h and 29.926 g/m^2/h at 4 weeks and 6 weeks after the injection, respectively. Furthermore, the patient exhibited a reduction in pigmentation of the lips, accompanied by an enhancement of the rosy hue. The spectrophotometric assessment revealed an increase in lightness (L*) from 44.35 to 47.56 and an increase in redness (a*) from 12.42 to 23.56 (Figure 2). The patient expressed satisfaction with the outcome.

Discussion

The term "cheilitis" refers to the inflammation of the lips, and its etiology may be attributed to a variety of conditions.[6,7,17] Lugović-Mihić et al[7,18] developed a classification system for cheilitis that took into account both the duration and the etiology of the condition, thereby distinguishing between three primary types: reversible cheilitis, irreversible cheilitis, and cheilitis associated with other cutaneous or systemic disease. The most prevalent forms of cheilitis are reversible cheilitis, which is transient in nature and is often amenable to treatment. Conversely, irreversible types of cheilitis are uncommon, more challenging to treat, and require confirmatory histopathological examination of an

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inflamed lesion. A list of cutaneous and/or systemic diseases associated with cheilitis includes pemphigus, lichen planus, Stevens-Johnson syndrome/toxic epidermal necrolysis, Sjogren syndrome, and angioedema, among others.

According to the study by Blagec et al,[6] cheilitis simplex is one of the most common subtype (28.5%) among the reversible cheilitis. It is characterized by the presence of cracked lips, lip fissures, or desquamation, typically on the lower lip.[7,18] These symptoms can be accompanied by a burning sensation and pain in the fissure, and prolonged manifestations may result in the formation of crusts or bleeding.[18] While the etiopathogenesis remains unclear, study by Wang et al[19] demonstrated that patients with cheilitis simplex exhibited impaired skin barrier function, as evidenced by the heightened passive diffusion of water through the stratum corneum (TEWL) and the diminished water content of the stratum corneum (capacitance). The habit of licking the lips, especially in patients with atopic dermatitis, can result in the removal of the thin, oily surface film that serves to protect the lips from moisture loss.[7] This results in an increased vulnerability to irritants,[20] including saliva, which contains digestive enzymes that can irritate the delicate skin of the lips.[17,20] Other frequent triggers include repeated lip biting, wiping habits, open-mouthed breathing, exposure to cold, windy, and dry weather, and mechanical trauma due to wind instrument or snorkeling equipment.[6,7,18,20]

One other subtype of reversible cheilitis that was frequently encountered was the contact/eczematous cheilitis,[6] which was attributed to contact irritants or allergens, including but not limited to oral hygiene products, lipsticks, or other materials that are routinely introduced into the oral cavity.[18] The utilization of patch testing is essential for the confirmation of allergic reactions that may underlie this condition.[7,18] Contrary to the prevalent notion that exfoliative cheilitis is synonymous with cracked lips,[18] it is imperative to acknowledge that it constitutes a distinct subtype of reversible cheilitis, characterized by persistent lip desquamation and peeling. This condition is often observed in individuals with B12 or iron deficiencies.[7,18] Other forms of reversible cheilitis include drug-induced cheilitis, triggered by medications such as isotretinoin, and angular cheilitis, manifesting at the corners of the lips and caused by nutritional deficiencies, infective agents, hypersalivation, or other factors.[7,17,18] In this patient, other subtypes of reversible cheilitis were excluded due to the normal result of the previous patch testing, along with the absence of malnutrition, iron deficiency, history of drug intake, and lesions at the corners of the lips—all of which supported the diagnosis of cheilitis simplex.

The treatment of cheilitis simplex typically address environmental or behavioral factors that contribute to its development and the application of emollients or occlusive such as lip balms and petroleum jelly whenever the lips felt dry.[7,20] However, it is noteworthy that certain ingredients present in lip balms have the potential to induce contact dermatitis. These include fragrances and flavorants (menthol, camphor, cinnamon, peppermint oil, vanilla, geraniol), dyes, preservatives, colophony, and others.[20] The utilization of low-potency corticosteroid ointment may be considered in select cases.[7] At present, the need for innovative therapeutic interventions capable of facilitating hydration from within the dermis, as opposed to merely being topically applied, has increased.[1]

The term “skin booster” has lacked a clearly delineated scope; however, it is generally understood to include all ingredients that, when injected or applied to penetrate the dermis, exert an influence on skin rejuvenation.[9,21] Five main ingredients that are commonly used as skin boosters include HA, deoxyribonucleic fragments (PN and polydeoxyribonucleotide), poly-L-lactic acid (PLLA) and polymer d-lactic acid (PDLA), growth factors, and exosome.[21] However, when the skin booster is specifically injected into the lips with the objective of improving the overall condition of the lips without causing any alteration of the lip volume, the term “lip booster” may be more appropriate.[10–12]

Hyaluronic acid is a naturally occurring polysaccharide that is found in the extracellular matrix of the dermal layer of the skin.[9,22] It is well-known for its ability to retain moisture, support hydration, and stimulate the secretion of growth factors within the skin’s connective tissues.[9] With regard to hydration, each HA molecule possesses the capacity to bind with up to 218 water molecules, with one gram of HA able to bind up to six liters of water.[9,23] This results in the water being maintained within the extracellular space, thereby playing a pivotal role in the prevention of skin dryness.[9,23] The moisture provided by HA serves to alleviate the presence of increased TEWL and decreased water content in the stratum corneum of the lips, which are present in cheilitis simplex.[19]

While cross-linked HA is primarily utilized as a filler for wrinkles and volume augmentation,[24] non-cross-linked HA is associated with its capacity to promote biorevitalization.[23] Biorevitalization focuses on enhancing skin hydration and stimulating fibroblast activity, thereby stimulating collagen and elastin production and giving a more youthful

appearance.[23,25] Non-cross-linked HA has been demonstrated to exhibit reduced volumizing effects and to diffuse well into peripheral tissues, rendering it suitable for the moisturization of thin and dry areas, such as the lips and eye regions.[9,13,22] However, its duration is comparatively brief when contrasted with that of cross-linked HA,[9] with breakdown of non-cross-linked HA by endogenic hyaluronidase occurred within 2–3 weeks after injection.[26] The presence of pain and moderate swelling after the injection, especially with higher HA concentration, has been observed in many cases of non-cross-linked HA utilization.[9,10,26]

To date, only three studies have utilized non-cross-linked or minimally cross-linked HA to enhance lip hydration. Adel's[13] research examined the use of a HA skin booster for the treatment of dry and dull-looking lips without volumization in 50 patients. However, the study did not assess the use of the hyaluronic acid skin booster as a standalone agent. Rather, it evaluated its combination with polydioxanone smooth threads. The patient was administered a 1-mL injection of 2% minimally cross-linked HA using a 22 G, 50 mm cannula, resulting in a significant enhancement of the fissures, cracks, and lip elasticity, with these effects persisting for a period of up to nine months following the injection. Adel[11] also utilized a combination of 1.5% non-cross-linked HA in conjunction with low-level laser therapy (LLLT) for the purpose of lip hydration in 20 patients. This approach resulted in enhancements in lip elasticity and smoothness that persisted until the conclusion of the three-month follow-up period. In the most recent study, Adel[12] utilized a 2.2-mL mixture comprising 1 mL of 1.5% non-cross-linked HA, 1 mL of 1.8% polydeoxyribonucleotide (PDRN), 0.1 mL of a plant-based exosome and PDRN mixture, and 0.1 mL of a 0.6% non-cross linked HA rejuvenating complex, injected to 30 patients. It showed enhancements to lip texture, increased hydration, and intensified rosy coloration of the lips up to three months after the injection. In this particular case report with cheilitis simplex, the patient reported an increase in hydration, which reached its peak at two weeks after injection, as indicated by a decrease in TEWL (from 34.386 $g/m^2/h$ to 26.218 $g/m^2/h$). This phenomenon coincided with the degradation of non-cross-linked HA. Nonetheless, the hydration levels remained superior (29.926 $g/m^2/h$) to the baseline level through the conclusion of the six-week observation period, a finding that may be attributable to the effects of the PN.

Polynucleotides are long-chain polymers made up of nucleotide monomers; these monomers are the basic building blocks of nucleic acids, such as deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).[1] PN exhibits several distinguishing characteristics that set it apart from PDRN. Primarily, it possesses longer nucleotide chains, higher molecular weight, and greater viscoelasticity in comparison to PDRN. It is derived from testes (gonads) rather than sperm DNA of trout or salmon, and it contains a scaffold structure that enables PN to maintain its integrity and provides structural support.[1,8,9,27] Intradermal injection of PN is postulated to normalize the physiological environment of the skin by restoring the normal efficiency of dermal fibrocytes.[28]

While the precise mechanism of action of PN remains to be elucidated, due to the molecular similarity between PN and PDRN, it has been postulated that the mechanism of action of PN may be analogous to that of PDRN.[9] The high water-binding capacity of PN, in conjunction with its trophic action on dermal fibroblasts, enables it to plump the extracellular matrix, thereby enhancing skin elasticity and turgor,[1,8] resulting in improvement of lip hydration in this patient. With respect to the issue of pigmentation, the present case report hypothesizes that PN is the underlying mechanism responsible for the observed changes. A review by Lampridou et al,[15] demonstrated that PN can reduce pigmentation in post-inflammatory hyperpigmentation and overall skin tone, and increase hemoglobin levels on acne scars and nasolabial folds. This decline in pigmentation and rise in hemoglobin levels may be reflected by the rise in L* (brightness) and a* (redness) values, respectively.

The utilization of PN to augment lip hydration has been examined in two studies. Rho et al[1] employed 2% PN injections for the treatment of dry and chapped lips in 30 patients, administered thrice with a three-week interval between injections over a period of nine weeks. This intervention led to a reduction in wrinkles and roughness of the lips. The study by Adel,[10] which utilized a single 2% PN injection to treat dry lips in five patients, yielded notable outcomes, which were increased hydration and enhancement of lip texture. This effect persisted for a duration of up to six months following the injection based on the clinical appearance and patients' subjective evaluation. In this case report, the hydrating effect of PN is demonstrated by the prolongation of the hydrating effect on the lips up to six weeks, despite the degradation of non-cross-linked HA already occurring at

approximately two to three weeks after injection. The impact on lip pigmentation manifested for patients at two weeks following the injection and persisted until the conclusion of the study period, and further supported by objective evaluation using spectrophotometer.

The lips and fingertips are regions of the body that contain a greater density of nerve endings, rendering them particularly sensitive to pain and other sensory stimuli.[29] Therefore, the incorporation of 0.3% lidocaine as an anesthetic agent in the lip booster has the capacity to mitigate discomfort during the injection process, thereby enhancing patient satisfaction.[30] In this case report, subsequent pain experienced after the procedure using 1% PN, 1% HA, and 0.3% lidocaine was transient and significantly alleviated after 30 minutes, and the patient felt that the procedure was relatively pain-free.

The utilization of 1% PN, 1% HA, and 0.3% lidocaine injection can be regarded as an alternative treatment option for cases of cheilitis simplex that do not respond to conventional topical treatments. This treatment is characterized by its practicality, requiring only a single injection, and its relative lack of discomfort, made possible by the addition of 0.3% lidocaine. The beneficial effect on hydration and pigmentation was sustained over an extended period and was objectively substantiated by the results obtained from the LDGS, tewameter, and spectrophotometer.

While this is the first case report to utilize the combination of non-cross-linked HA and PN for increasing lip hydration, the present case report is subject to certain limitations. Firstly, the measurement with TEWL should be interpreted with caution. An additional measurement of capacitance, which reflects the water content of the stratum corneum,[19] may serve as a useful supplementary indicator of lip hydration. Secondly, in comparison with previous studies, lower concentrations and different combinations of active ingredients were utilized in this study. However, the investigation was conducted in a particular case of cheilitis simplex, with the objective of identifying an optimal lower concentration capable of achieving a beneficial effect, as demonstrated by objective measurement on hydration and pigmentation. Lastly, the duration of the follow-up in this case report is brief. The observed transient nature of the hydrating impact of the injection suggests the potential necessity for additional treatment modalities. These might include the incorporation of lip balms as needed or the repetition of the injection at designated intervals. A thorough discussion of these potential treatment options is warranted and should be pursued. Therefore, further study with a longer follow-up period and a larger number of patients is necessary to confirm the findings in such case report.

Conclusion

This is the first case report that used a single injection comprising 1% PN, 1% non-cross-linked HA, and 0.3% lidocaine for the treatment of cheilitis simplex that demonstrated resistance to the conventional topical treatment. This relatively pain-free treatment has been shown to be both efficacious and practical, with the additional benefit of enhancing the pigmentation of the lips. Further studies involving longer follow-up period and more patients are required to confirm the findings.

Ethics Approval and Informed Consent

Prior to the publication of this case report, written informed consent was obtained from the patient, who granted permission for the use of photographs and medical data. Additionally, institutional approval was obtained from the Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung with approval number DP.04.03/D.XIV.4.4/2990/2025.

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Disclosure

The authors report no conflicts of interest in this work.

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