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Case Report

Safety and aesthetic outcomes of using fillers with different cross-linking agents. A case report.

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DISCLOSURE: **ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.**

Of the several dermal fillers developed in recent decades, hyaluronic acid fillers have become the material of choice. They are safe, long-lasting, non-immunogenic, available to most patients, and can be removed with hyaluronidase. Unfortunately, early and delayed complications can also occur after HA filler injection. Below, we present the case of a 42-year-old patient who had complications after the aesthetic procedure using hyaluronic acid dermal fillers in the past. Surprisingly, the treatment performed with hyaluronic acid cross-linked with another cross-linking agent was without complications. The affected places were the chin and malar area. In 2021, after performing augmentation with hyaluronic acid in the chin area, a patient developed swelling, which subsided after using hyaluronidase (Hylase Dessau 300 I.E.) and corticosteroids. The patient repeated the procedure in 2022, where she was administered 2 ml of hyaluronic acid in July 2022. About 3 weeks after injection, oedema and nodules appeared at the injection site in the zygomatic/malar area; after using Prednisone, the changes subsided. In September 2022, 3 ml of PEG-cross-linked hyaluronic acid was successfully performed with no side effects. In the described case, an important role was played by the ability of the hyaluronic acid hydrogel to modulate human immunological functions, which was associated with a very low risk of immune-related side effects and accompanying cellulitic processes.

INTRODUCTION

Hyaluronic acid (HA) is a naturally occurring biopolymer, mainly concentrated in the extracellular matrix of soft connective tissue, dermis, the vitreous body of the eye, hyaline cartilage, synovial fluid, nucleus disc and umbilical cord. It has unique and unmatched chemical-physical properties and is characterised by numerous biological functions (1). HA is a biodegradable, biocompatible, non-toxic, and non-immunogenic polymer. In its naturally occurring form, HA has a short half-life (usually 1–2 days) and is eliminated by the lymphatic system and liver. To improve the stabilisation of HA, control of its degradation rate and obtain a more stable material - while maintaining its properties - various strategies are used, among which cross-linking and conjugation stand out. HA reacts with a cross-linking agent that can form covalent bonds between HA chains during cross-linking. Therefore, chemical cross-linking of HA is necessary to extend its residence time in the dermis (2).

HA has been used in medicine for many years in various applications (scaffolds in tissue engineering, in the treatment of osteoarthritis, ophthalmic surgery, etc.), and in recent decades it has been used as a primary tool in aesthetic medicine clinics. HA is on the market in several pharmaceutical forms, including nanoparticles, nanocomplexes, matrices, and hydrogels (3). Hydrogels based on hyaluronic acid (HA) have been very popular since the first years of the new millennium. Regarding dermal fillers, the introduction of HA-based fillers has been a significant paradigm shift in the field, moving from permanent or semi-permanent fillers to biodegradable ones such as those based on hyaluronic acid. The latter property has prompted the chemical modification of HA to reduce the rate of biodegradation and allow the viscoelastic properties to be modulated for compatibility with various tissues; the most successful chemical modification was achieved using cross-linking agents, i.e., chemical compounds that bridge two sections of the HA chain. Several cross-linking compounds have been introduced: 1,4-butanediol diglycidyl ether (BDDE), 1,2,7,8-diepoxyoctane (DEO), divinyl sulfone (DVS), hexamethylenediamine (HMDA) and polyethylene glycol diglycidyl ether (PEGDE). Both the cross-linking agent used and the cross-linking parameters play an important role in determining the physico-chemical properties of the hydrogel, which are of great importance in clinical applications (4).

CASE REPORT

We present the case of a healthy 42-year-old woman who received HA injections several times starting in 2021. In 2021, an adverse reaction of unknown origin occurred once after application in the chin area. After the hyaluronic acid augmentation procedure (HA-BDDE) in the chin area, there was swelling, which subsided after using Hylase and corticosteroids. A year later (in 2022), she repeated the procedure, injecting 2 ml of cross-linked BDDE hyaluronic acid in the zygomatic/malar area. About 3 weeks after injection, oedema and nodules appeared at the injection site in the zygomatic/malar area (Fig. 1 a, b, c). No disturbing changes were observed in other places except where hyaluronic acid was administered, and no enlarged adjacent lymph nodes were noticed. The patient was given Prednisone in decreasing doses, starting with 60 mg orally per day, then 50-40-30-20-10 mg per day, and the lesions resolved. In the same year (2022), despite our concerns, after discussing the benefits and risks of a new injection, the patient decided to repeat the treatment with HA injections in the area in the zygomatic/malar area, this time choosing hyaluronic acid cross-linked with PEG (polyethylene glycol). The patient tolerated the procedures well, with no adverse events related to treatment (Fig. 2 a, b). For the treatment I used (for each side):

- Neauvia Stimulate (Matex Lab, Switzerland) 0.5 ml - lateral lower cheek/parotid area to addressee the sunken area at the parotid level and pre auricular volume loss, it lifts the jawline;
- Neauvia Stimulate (Matex Lab, Switzerland) 0.5 ml - submalar to address the sunken area and improve volume loss in the submalar area;
- Neauvia Rheology (Matex Lab, Switzerland) 0.5 ml to correct the mental curve and give projection to the chin.

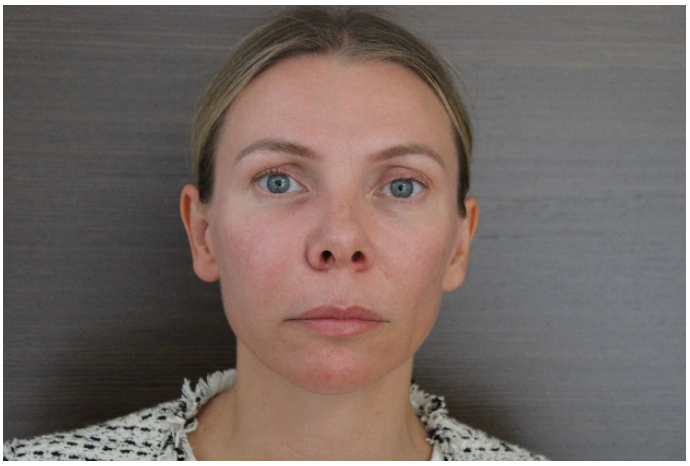

Fig. 1a. *Condition 3 weeks after surgery, oedema and nodules appeared at the zygomatic/malar area injection site.*

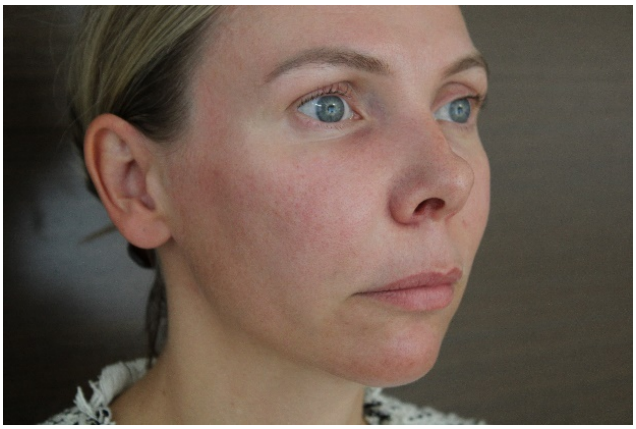

Fig. 1b. *Condition 3 weeks after surgery, oedema and nodules appeared at the zygomatic/malar area injection site.*

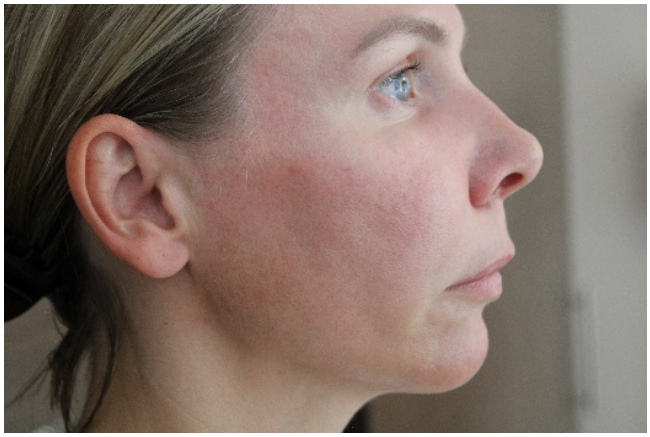

Fig. 1c. *Condition 3 weeks after surgery, oedema and nodules appeared at the zygomatic/malar area injection site.*

Fig. 2a. *Before and after injecting hyaluronic acid cross-linked with PEG, no adverse events related to treatment were reported.*

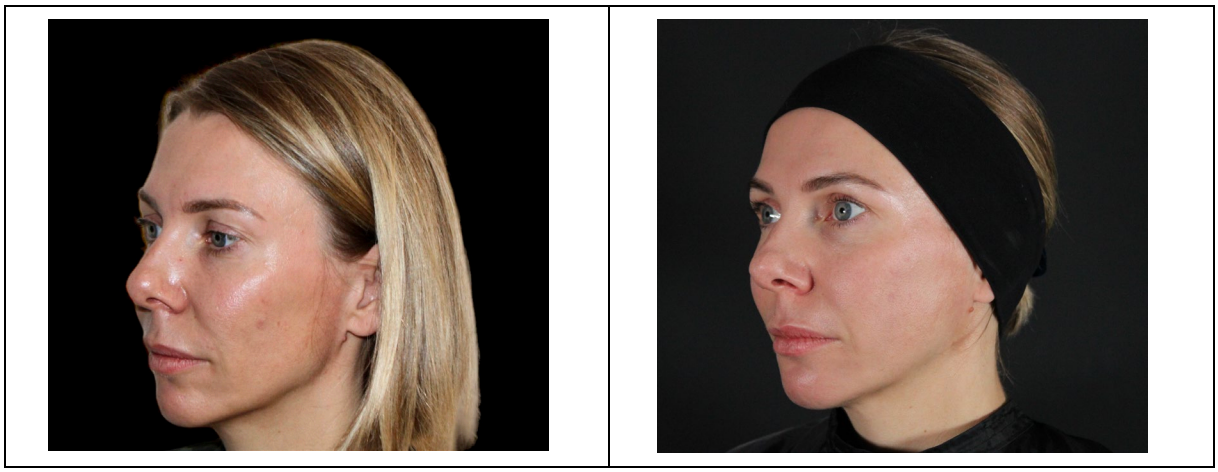

Fig. 2b. *Before and after injecting hyaluronic acid cross-linked with PEG, no adverse events related to treatment were reported.*

DISCUSSION

Dermal fillers, based on hyaluronic acid and other substances, injected into the tissues induce the inflow of phagocytic neutrophils and mononuclear cells through concentrated macrophages and activation of fibroblasts. Such a process is natural as the immune system cannot enzymatically break down or phagocytize the foreign body. In the case of HA, the cross-linking process of the molecule increases its size, which prevents phagocytosis and stimulates a chronic cellular response (5).

To minimise the possibility of side effects, apart from obvious matters, such as maintaining all procedures related to the treatment itself, we should pay attention to the selection of the product itself, which is of key importance. PEGylated HA fillers reduce the local immune response, suggesting not only that PEG-HA does not carry a significant pro-inflammatory risk effect on PMNs, but also that it can effectively modulate PMN functions, resulting in anti-inflammatory effects. Such properties may contribute to the beneficial effects of PEG-HA in various medical and cosmetic applications (6).

CONCLUSION

The article describes a case of complications after using a cross-linked HA filler. We also wanted to emphasise what happened during the last application of the HA filler, cross-linked with another cross-linking agent, and how cross-linking technologies can affect the outcome of the treatment or potential adverse reactions.

HA-based hydrogels are generally considered safe and well-tolerated, but recent evidence increasingly points to emerging safety issues related to their immune function, including delayed hypersensitivity and granulomatous reactions (7, 8).

In the case of the described patient, the reaction was limited only to the place of application of the preparations in the chin area and the zygomatic/malar area in 2021 and June 2022. The last treatment in a short time after the complication - the application of HA filler (this time cross-linked with PEG, and not as in the previous two administrations of BDDE) did not cause any complications short and longterm, which makes the hypothesis of an individual immune response to the administered product probable. The available literature indicates that it is impossible to predict the effect of glycosaminoglycan-based hydrogels on immune system cells solely based on their chemical composition because even small differences in chemical

structure and proportions of ingredients may ultimately have different and sometimes opposing effects. Jeong et al. showed that in vitro PEG-crosslinked hyaluronic acid-based fillers have high biosafety and reduced immune cell recruitment, reactive oxygen species (ROS) production, and pro-inflammatory cytokine (mRNA) expression (9, 6).

In the described case, an important role was played by the ability of the PEG-crosslinked hydrogel to modulate human immunological functions, which was associated with a very low risk of immune-related side effects and accompanying cellulitic processes (6).

Informed Consent Statement

Informed consent was obtained from the subject involved in the case report. Written informed consent has been obtained from the patient to publish this paper.

The case report was conducted in accordance with the Declaration of Helsinki.

Conflicts of Interest

The author declares no conflicts of interest.

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