
Cutaneous Hypersensitivity Reaction to Injectable Hyaluronic Acid Gel

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BACKGROUND. Injectable hyaluronic acid gel is a nonanimal biomaterial used for soft tissue augmentation.

OBJECTIVE. The dermal implantation of this naturally occurring polysaccharide is reported to be well tolerated by patients, with a longer duration in tissue than bovine collagen without any major local or systemic side effects. We report a case of an acute hypersensitivity reaction in a woman after her third injection for improvement of melolabial fold wrinkles.

METHODS. An adverse granulomatous-like response to the intradermal injection of a modified hyaluronic acid gel is described.

RESULTS. The patient developed indurated and erythematous papulocystic nodules in the melolabial folds bilaterally at the sites of injection.

CONCLUSION. Injectable hyaluronic acid gel can be associated with severe allergic reactions and patients should be warned of this possible treatment side effect.

INJECTABLE HYALURONIC ACID GEL is one of the latest biomaterials developed for soft tissue augmentation/volume expansion.¹ Although not currently approved by the U.S. Food and Drug Administration (FDA), it is commonly used in Europe and Canada for correction of soft tissue defects and improved facial contouring. Hyaluronic acid is a naturally occurring polysaccharide,² a glycosaminoglycan composed of the repeating disaccharides D-glucuronic acid and N-acetyl-D-glucosamine.¹⁻³ This compound is a member of a class of substances forming part of the "ground substance" or extracellular matrix of the dermis and functions to provide support for other tissues.³ Hyaluronic acid has natural hydrating functions with an ability to bind large volumes of water. This molecule can be modified to form an insoluble, cross-linked, high-viscosity gel which is suitable for dermal implantation.^{2,4} Previous studies have not demonstrated any serious adverse effects or allergic reactions to this filler material. This apparent lack of sensitization is thought to be due to the fact that the product is of nonanimal origin and should therefore be devoid of any antigenic-stimulating peptides.^{1,4} We report the case of a woman developing an acute hypersensitivity reaction at the sites of injection of a modified hyaluronic acid biopolymer gel.

Case Report

A 54-year-old Caucasian woman underwent treatment for prominent facial lines and wrinkling with the in-

tradermal injection of a modified hyaluronic acid gel. She was first treated in April 1998 and then again in November 1998 with an excellent cosmetic result and without any adverse effects. She did not undergo any pretreatment skin testing for evidence of hypersensitivity to the injected material. In June 1999 the patient again sought treatment for recurrent wrinkling of her melolabial folds and proceeded with her third round of hyaluronic acid injections. Each treatment session involved several intradermal injections in a continuous row along the melolabial folds. She experienced mild bruising and erythema at the injection sites after each treatment that resolved within 1–2 days. Two weeks after the third series of injections, however, the patient developed acute multiple, tender red nodules within the treatment areas.

Physical examination showed multiple, discrete nodules in the bilateral melolabial folds. The papulocystic nodules measured 0.5–1 cm in diameter and were in various stages of development. Some nodules exuded a coagulated, yellow, stringy material and appeared to be secondarily infected with frank pus. Other lesions were more indurated, almost fibrotic, with significant erythema but still with intact overlying skin (Figure 1). A bacterial culture of the draining cystic nodules was obtained but failed to grow out any pathogenic bacteria. The patient declined a diagnostic biopsy given the location of her eruption.

The patient was treated with minocycline 250 mg by mouth twice a day for 1 week and methylprednisolone 4 mg by mouth once a day for 6 days to help reduce the inflammatory response and prevent permanent scarring. The patient also applied warm saline compresses twice a day to the affected areas and the most purulent and fibrotic nodules were injected with triamcinolone acetonide 5 mg/cc for symptomatic re-

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Figure 1. Initial presentation demonstrating multiple erythematous cystic nodules in the bilateral melolabial folds.



Figure 2. Clinical appearance after treatment, with marked improvement of cutaneous nodules with residual postinflammatory hyperpigmentation.

lief. The patient rapidly cleared on this regimen, with only minimal postinflammatory hyperpigmentation at the sites of the larger, open cystic nodules (Figure 2). Two weeks later the patient returned with recurrent inflammation in the right melolabial fold with early eruption of tender, discrete nodules in previously inactive sites. The patient was again treated with intralesional corticosteroids and warm compresses with rapid resolution of her symptoms.

Discussion

Injectable materials suitable for soft tissue augmentation and volume expansion have been studied for more than 40 years and have included silicone, paraffin, and collagen.^{5,6} Since its approval in the early 1980s, however, bovine collagen has been the mainstay of therapy for correction of facial contour defects, atrophic scars, and wrinkles.^{6,7} Collagen implants are temporary fillers and their use has been associated with major adverse tissue effects. Approximately 3% of patients will experience an allergic reaction to injected bovine collagen with development of circulating antibodies to the foreign material.⁵⁻⁹ This reaction usually subsides within 6 months, but has been reported to last up to 18 months in some people.⁷ Double skin testing is therefore recommended, but not required, prior to treatment with collagen to monitor for this allergic response.¹⁰

Localized skin necrosis is another potential side effect associated with collagen injections. Necrosis is especially common in the glabellar area and results from occlusion of blood vessels during injection.^{5-7,9} In addition, the beneficial clinical effects obtained with bo-

vine collagen implants will usually only last up to about 6 months before supplemental treatments are necessary.⁷ In response to the need for safer and longer lasting biomaterials for filling of soft tissue defects, a modified hyaluronic acid gel was developed. Two forms of this polymer are currently available.

Hyaluronic acid is a glycosaminoglycan which naturally occurs in the skin as part of the extracellular matrix. It is assembled as disaccharide units containing glucuronic acid alternating with N-acetylglucosamine.¹⁻³ Hyaluronic acid has a high molecular weight and because of its water-binding affinity can form a hydrated polymer with a high viscosity. The hyaluronic acid can be modified to form a more insoluble, more highly cross-linked molecule for improved biocompatibility and longer presence in the tissue.¹ Modified hyaluronic acid gel has an "isovolemic pattern" of degradation whereby it can maintain its original volume over time even with decreasing concentration of implant. The molecule is able to bind more water as the implant is degraded and therefore can maintain a somewhat constant volume over time. Eventually the implant is fully degraded and only then is re-treatment needed.¹ Thus these bioengineered hyaluronic acid implants seem to be superior to traditional bovine collagen implants in terms of tissue longevity. Some studies have demonstrated the presence of modified hyaluronic acid gels in tissue a full year after injection.⁴

Previous studies with both hylan b gel implants and modified hyaluronic acid gel have shown them to be well tolerated and safe in patients without any serious adverse effects.^{1,4} The most common adverse reactions were self-limited and included bruising, erythema,

edema, and slight discomfort at the treatment sites. Most of these reactions resolved within 1–3 days and there have been no reported cases of systemic effects or cutaneous hypersensitivity.¹ Hyaluronic acid is believed to be nonimmunogenic² and therefore routine skin testing for allergy is not currently recommended. This gel is made in culture by bacterial fermentation, however, and if any impurities are present in its manufacturing, then these could account for a sensitization reaction.¹

This is the first reported case of a patient developing an acute hypersensitivity reaction to locally injected hyaluronic acid gel. Despite previous reports to the contrary, injectable hyaluronic acid gel may be capable of producing an allergic-type reaction. Even if this patient had been skin tested for allergy, no reaction would have been elicited since she did not develop symptoms until after her third treatment. As more patients undergo treatment with injectable hyaluronic acid it may become possible to estimate the incidence of this adverse reaction and whether this is a true allergy to some component of the modified hyaluronan or merely to impurities present as a result of fermentation. Until the issue can be more fully evaluated, patients should be warned of this potential complication. Our patient will continue to be monitored for recurrence of inflammation since this reaction pattern

will likely persist until all of the implanted hyaluronic acid has been fully degraded.

References

1. Duranti F, Salti G, Bovani B, Calandra M, Rosati ML. Injectable hyaluronic acid gel for soft tissue augmentation. *Dermatol Surg* 1998;24:1317–25.
2. Goa KL, Benfield P. Hyaluronic acid. A review of its pharmacology and use as a surgical aid in ophthalmology, and its therapeutic potential in joint disease and wound healing. *Drugs* 1994;47:536–66.
3. Gallo RL. Proteoglycans and glycosaminoglycans of skin. In: Freedberg IM, Eisen AZ, Wolff K, et al., eds. *Fitzpatrick's Dermatology in General Medicine*. New York: McGraw-Hill, 1999:283–4.
4. Piacquadio D, Jarcho M, Goltz R. Evaluation of hylan b gel as a soft tissue augmentation implant material. *J Am Acad Dermatol* 1997;36:544–9.
5. Elson ML. Soft tissue augmentation. A review. *Dermatol Surg* 1995;21:491–500.
6. West TB, Alster TS. Human-derived and new synthetic injectable materials for soft tissue augmentation: current status and role in cosmetic surgery. *Plast Reconstr Surg* 1999;in press.
7. Pollack SV. Silicone, fibrel, and collagen implantation for facial lines and wrinkles. *J Dermatol Surg Oncol* 1990;16:957–61.
8. McCoy JP, Schade WJ, Siegle RJ, Waldinger TP, Vanderveen EE, Swanson N. Characterization of the humoral immune response to bovine collagen implants. *Arch Dermatol* 1985;121:990–4.
9. Stegman SJ, Chu S, Armstrong RC. Adverse reactions to bovine collagen implant: clinical and histologic features. *J Dermatol Surg Oncol* 1998;14(suppl 1):39–48.
10. Klein AW. In favor of double testing. *J Dermatol Surg Oncol* 1989;15:263.
11. Restylane. Investigators brochure. Uppsala, Sweden: Q-Med AB, 1996.