

Delayed Hypersensitivity Reaction to Restylane®

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This case report documents the first known case of a delayed hypersensitivity reaction to Restylane®. The patient experienced typical symptoms of a delayed hypersensitivity reaction to soft tissue augmentation materials. Serum testing was negative, and biopsy of skin testing in the arm demonstrated a typical delayed hypersensitivity reaction.

This case report discusses treatment with hyaluronidase and other modalities in the first demonstrated hypersensitivity reaction to a hyaluronic acid injectable material.

With the advent of Zyderm® 1, the first material for soft tissue augmentation, the search for the perfect wrinkle filler began. Since the US Food and Drug Administration's approval of this filler in 1981, many materials have been introduced worldwide for filling tissue defects. Of the many fillers on the market, none meets all the criteria of a perfect filler. The hyaluronic acid group of fillers is among the most versatile and meets most of the criteria of a perfect material, among which nonallergenicity is primary. This article describes the first known delayed hypersensitivity reaction to Restylane®, a popular hyaluronic acid–derived filler.

CASE REPORT

The patient was a 56-year-old white woman who requested soft tissue augmentation for various areas of her face. She had never undergone treatment with any filler. On August 18, 2006, she was injected with 2 cc of Restylane for tear troughs, undereye lines and contour, vermilion border, oral commissures, and nasolabial folds. The patient was happy with the results, and no adverse

events were noted. On December 8, she was again treated with 1 cc of Restylane under both eyes and in the oral commissures and the chin fat pad area. Once again, the patient was happy with the results and experienced no adverse events.

On February 9, 2007, the patient reported that for approximately one week she had been experiencing intermittent lumps in and swelling of the injection areas around the mouth, mostly the oral commissures and chin. Examination revealed inflammation that was slightly tender to the touch. On February 16, she reported that the areas were now more painful and exhibited increased erythema and swelling with nodule formation.

On February 19, the patient reported further extension of the reactive areas in the oral commissures and chin and now included the nasolabial folds and vermilion border (Figures 1 and 2). On March 26, she noted new reactive areas under both eyes (Figure 3). Her symptoms, including their delayed onset, were reminiscent of allergic responses that have been reported with the use of bovine collagen.¹⁻³

Blood tests for immunoglobulins E and G anti-Restylane antibodies by the Johns Hopkins University Dermatology, Allergy and Clinical Immunology Reference Laboratory were negative. The patient underwent intradermal testing with 0.04 cc of Restylane to the right upper arm on March 26, and a punch biopsy was obtained on March 30 and submitted to the department of pathology at Brigham and Women's Hospital. Pathologic examination revealed a reticular dermal deposit of amorphous

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Figure 1. Typical allergic reaction to filling material in the nasolabial folds.

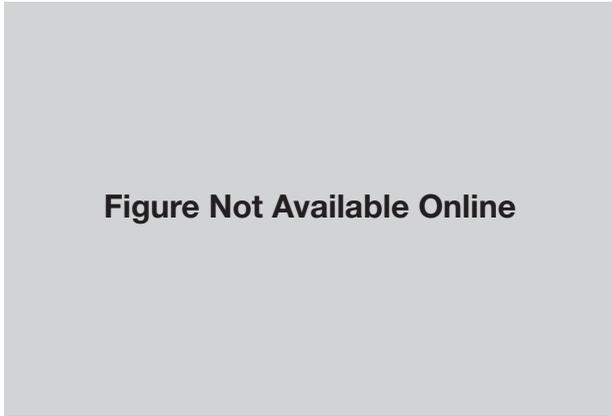


Figure 2. Full-face photograph of a delayed hypersensitivity reaction to Restylane®.

material that was consistent with hyaluronic acid with peripheral lymphoeosinophilic infiltrate. The interpretation was that the inflammatory response suggested a delayed hypersensitivity reaction at the injection site.⁴⁻⁶ This response was, of course, compatible with a delayed hypersensitivity reaction, with negative serologic testing and tissue reaction demonstrated on biopsy at least 72 hours after intradermal injection.

MANAGEMENT OF THE ALLERGIC RESPONSE

Treatment began on February 19 with intralesional injections of hyaluronidase to the reactive areas around the mouth. For treating the left and right sides of the oral commissures and an area of the vermilion border, 30 U was injected. After 20 minutes, an additional 30 U was injected into these areas, including the chin. After another 20 minutes, an additional 22 U was injected; also, 6 mg of betamethasone was injected intramuscularly (IM). The patient complained only of some mild burning and tenderness at the injection sites. Palpation of the treated reaction sites revealed some softening of the nodules almost immediately. Examination a day later revealed mild erythema and soft, more pliable areas of edema where nodules had been. The patient reported that these areas had become “hot, red, and inflamed” overnight but had “calmed down” that morning.

On March 5, examination revealed persistent erythema and edema at all the previously treated areas and a new area at the left nasolabial fold. Twenty units of hyaluronidase was injected to a persistent area of the right oral commissure: 10 U to an area of the left oral commissure and 10 U to the left nasolabial fold, where the new reactive area was starting. Forty-eight hours later, these sites were still erythematous and firm on palpation. In case of bacterial contamination, 6 mg of betamethasone was injected IM, and 500 mg of levofloxacin was administered.

On March 26, the treated sites appeared to be improving, but an area in the right oral commissure and another in the left nasolabial fold were still erythematous and firm. Fifteen units of hyaluronidase was injected into each site. New reactive areas were noted under both eyes; 15 U was injected under the left eye and 7.5 U into a small area under the right.

On March 30, examination of hyaluronidase-treated areas revealed dramatic improvement of perioral sites. Areas under both eyes continued to swell with erythema and firm nodules. Forty milligrams of triamcinolone acetonide was injected IM.

On April 9, examination once again revealed persistent areas of erythema and firm nodules under both eyes. Fifteen units of hyaluronidase was injected into the remaining nodules under both eyes. On April 23, new areas of erythema and nodules appeared under both eyes; 25 U of hyaluronidase was injected into the nodules under the left eye and 15 U under the right.

On May 4, improvement was noted, but nodules persisted under both eyes. An additional 40 U of

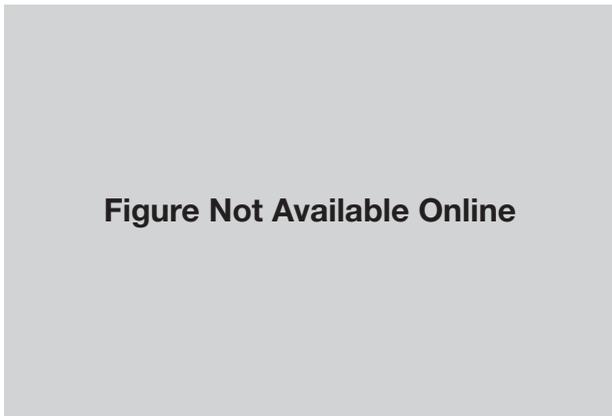


Figure 3. Erythema and edema under eyes after injection with Restylane®.

DELAYED HYPERSENSITIVITY REACTION

hyaluronidase was injected intralesionally under both eyes. A week later, 15 U was injected into the persistent nodules under the left eye and 10 U under the right. On May 12, the areas were still nodular and were again treated with 25 U under the right eye and 15 U under the left. Two weeks later, the patient complained of persistent swelling and pain under both eyes. On May 24, she received 6 mg of betamethasone again injected IM, and an additional prescription was given for 500 mg of levofloxacin once daily. On June 18, the perioral areas were free of reaction, but reactive areas were still apparent, although improved, under both eyes. Forty-five units of hyaluronidase was injected into the nodules under the left eye and 35 U under the right.

On June 25, examination revealed marked improvement, but some erythema and palpable nodules persisted under both eyes. Hyaluronidase was again injected: 25 U into the nodules under the right eye and 15 U under the left. Follow-up examinations and injections of hyaluronidase will continue weekly until the reaction completely resolves.

COMMENT

Although significant scientific advances have been made in developing materials for soft tissue augmentation, it must be remembered that any material injected into the cutaneous system may create an adverse event. Although hyaluronic acid is non-species specific,⁷ unlike bovine collagen, and occurs naturally, there are a number of methods by which a reaction may be manifested clinically.⁸⁻¹¹

In this case report, the patient demonstrated a delayed hypersensitivity reaction after a number of Restylane injection sessions. Pathologic examination suggested that this reaction was from the hyaluronic acid material and not another substance in the material, such as manufacturing-induced bacterial cell wall contamination.

Treatment for this type of delayed hypersensitivity reaction should consist of not only the same treatment method used for other delayed hypersensitivity reactions to injectable materials but also hyaluronidase to remove the offending material. It is fortunate that hyaluronidase

is available to hasten the removal of hyaluronic acid materials should an adverse event occur. Even with this valuable tool, however, an adverse event may erupt intermittently and linger for months. Almost any injected filler material may cause an adverse event, including a delayed hypersensitivity reaction such as the type described in this case report.

SUMMARY

With increasing worldwide use of injectable fillers for soft tissue augmentation, it is imperative to advise patients of possible reactions despite the benign nature of the implants. As important as this caution is for Restylane, it is even more important with injections of artificial polymers or materials that become permanent after injection.

REFERENCES

1. Elson ML. The role of skin testing in the use of collagen injectable materials. *J Dermatol Surg Oncol.* 1989;15:301-303.
2. Klein AW. In favor of double testing. *J Dermatol Surg Oncol.* 1989;15:263.
3. DeLustro F, Mackinnon V, Swanson NA. Immunology of injectable collagen in human subjects. *J Dermatol Surg Oncol.* 1988;14(suppl 1):49-55.
4. DeLustro F, Smith ST, Sundsmo J, et al. Reaction to injectable collagen: results in animal models and clinical use. *Plast Reconstr Surg.* 1987;79:581-594.
5. Cooperman LS, Michaeli D. The immunogenicity of injectable collagen, II: a retrospective review of seventy-two tested and treated patients. *J Am Acad Dermatol.* 1984;10:647-651.
6. Ellingsworth LR, DeLustro F, Brennan JE, et al. The human immune response to reconstituted bovine collagen. *J Immunol.* 1986;136:877-882.
7. Benedetti L, Cortivo R, Berti T, et al. Biocompatibility and biodegradation of different hyaluronan derivatives (Hyaff) implanted in rats. *Biomaterials.* 1993;14:1154-1160.
8. Lowe NJ, Maxwell CA, Lowe P, et al. Hyaluronic acid skin fillers: adverse reactions and skin testing. *J Am Acad Dermatol.* 2001;45:930-933.
9. Larsen NE, Pollack CT, Reiner K, et al. Hylan gel biomaterial: dermal and immunologic compatibility. *J Biomed Mater Res.* 1993;27:1129-1134.
10. Richter AW, Ryde EM, Zetterström EO. Non-immunogenicity of a purified sodium hyaluronate preparation in man. *Int Arch Allergy Immunol.* 1979;59:45-48.
11. Lupton JR, Alster TS. Cutaneous hypersensitivity reaction to injectable hyaluronic acid gel. *Dermatol Surg.* 2000;26:135-137. ■