Persistent Erythema After Human Collagen Filler Injections

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Collagen fillers have been become an increasingly popular means of cosmetic enhancement as individuals seek new ways to mask their wrinkles and augment their lips. This increased demand for soft tissue augmentation fosters the need for safer, more effective, longer-lasting methods and materials to ensure aesthetically pleasing outcomes. Human collagen fillers (eg, CosmoDerm and CosmoPlast) became attractive because of their theoretical zero risk of allergic reactions, such as the sensitivity that has been reported with bovine collagen fillers. We report 2 cases of prolonged clinical erythema and other symptoms of hypersensitivity following injections with human collagen fillers, as well as effective treatment modalities for these reactions.

With aging come inevitable changes in skin proteins and various repair mechanisms, leading to wrinkles and lines and making fillers increasingly popular as cosmetic treatment. The concept of soft tissue augmentation dates to 1893, when Neuber[1] became the first physician to remove fat from a patient's arms to fill facial defects. Some early means of soft tissue augmentation included using autologous fat, paraffin, bovine collagen, and injectable silicone.[2,3] Because the primary alterations in aged skin occur in the dermis, treatments have targeted primarily this region of the skin.

The first of the collagen fillers, Zyderm, a bovine collagen, was introduced in 1977 and approved by the US Food and Drug Administration (FDA) in 1981.[4] Early clinical studies of Zyderm revealed its effectiveness in concealing age-induced lines. However, the short duration of Zyderm made longer-lasting fillers desirable. Zyplast, a bovine collagen that is cross-linked with 0.0075% glutaraldehyde, was later developed; it demonstrated a longer-lasting clinical effect. Unfortunately, the body rapidly breaks down bovine collagen; most of its clinical effect is lost within 3 to 4 months, requiring patients to return for repeated injections to maintain a lasting clinical effect.[5,6] Three bovine collagen fillers are available in the United States: Zyderm 1, Zyderm 2, and Zyplast. These fillers comprise highly purified bovine dermal collagen (types 1 and 3) that is dispersed in phosphate-buffered, physiological saline solution containing 0.3% lidocaine.[7]

HYPERSENSITIVE ALLERGY TO HUMAN COLLAGEN FILLERS

As a xenogenic implant, bovine collagen requires skin testing before treatment because of its immunogenic potential. Elson[8] strongly recommended "that all patients being considered for soft tissue augmentation with bovine collagen injectable materials undergo double skin testing…[to] reduce the number of patients experiencing allergic reactions in cosmetically undesirable locations"; thus, double skin sensitivity tests became the standard before bovine collagen filler injections. Skin testing for all bovine collagen fillers is performed by subcutaneously injecting approximately 0.1 mL of Zyderm 1 into a visible area, such as the forearm, to allow patients to

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closely monitor for erythema, induration, pruritus, pain, or other symptoms of hypersensitivity.[9] Approximately 3% of patients will prove to be bovine collagen allergic with the first skin test[5]; however, some additional occurrences of hypersensitivity may be detected by performing a second skin test (often placed on facial skin at the hairline) approximately 4 weeks after the first negative test. Approximately 0.5% of patients present with allergy after the second test, which is usually monitored for an additional 2 weeks. Thus, the minimum observation period for both skin tests is 6 weeks before treatment.[2]

Patients with positive bovine collagen skin tests to Zyderm 1, sensitivity to lidocaine, or both are unable to use Zyderm and Zyplast. Interestingly, a considerably small number of patients who may have even 2 negative skin tests still experience hypersensitivity after injections with bovine collagen fillers.[6] Reported successful treatments of these reactions have included the use of steroids (topical, oral, and intralesional), oral histamines, oral cyclosporine,[10] or topical tacrolimus.[11] Nonallergenic reactions, such as erythema, ecchymosis, local necrosis, abscess formation, infections, and herpetic reactivation, are also possible with bovine collagen fillers.[2,9] Aside from this small risk of hypersensitivity, bovine collagen fillers have been used for 2 decades with remarkable success; many new fillers are compared to bovine collagen, as previously it has been considered the gold standard of injectable filler therapy in the United States.[12]

Despite the popularity and relative efficacy of bovine collagen fillers, researchers and physicians alike sought a filler that had a lower risk of hypersensitivity and a longer duration of effectiveness. Autologen, an autologous collagen dispersion, was used as a collagen filler, for it comprised only human, nonallergenic proteins.[5] To use Autologen, the patient's own skin was harvested during abdominoplasty or other aesthetic surgery, frozen in saline solution, and shipped on ice by overnight express mail to the manufacturer.[6] To prepare Autologen, which requires approximately 2 sq in of skin for 1 mL of 5% Autologen,[6] the epidermis was mechanically removed and the dermis minced to produce a suspension of dermal tissue matrix consisting primarily of fibrillar, nondenatured collagen.[13] Autologen was subsequently sent to the treating physician in 1-mL syringes and refrigerated for up to 6 months.[6] A patent for Autologen was secured in 1994 after 6 years of research.[3] The filler became attractive because patients' own collagen was used and also because of the theoretical lack of potential hypersensitivity; however, because of production complexities and the extensive harvesting techniques required in processing autologous skin, the manufacturer stopped production of Autologen and began producing Dermalogen, a homologous dermal suspension derived from tissue banks.[5]

In addition to Dermalogen, several other allogenic products were developed for soft tissue augmentation, including AlloDerm, Cymetra, Dermaplant, and Fascian. Dermalogen, introduced in 1998, is a human collagen from the dermal layer of donor skin with no added anesthetic. Compared with bovine collagen, this allogenic product had increased length of clinical effect by approximately 6 months. A 72-hour skin sensitivity test was recommended but not required.[6] Skin testing showed no benefit of Dermalogen over bovine collagen fillers, and the extended clinical effect was not viewed by aesthetic physicians as significant; hence, the product was taken off the market.

Because skin testing slows the initiation of collagen filler therapy, a completely allogenic, nonallergenic alternative was sought that did not carry the risk of disease transmission.[9] To fulfill this need, recombinant human collagen filler was advanced; theoretically, it had neither the potential for hypersensitivity nor the presence of any contaminants.[12] The CosmoDerm and CosmoPlast family of fillers was developed on the engineering of human fibroblastic collagen from a single cell line and grown in culture despite not being identical to human collagen found in human skin. Three formulations exist with collagen microfibrils suspended in phosphate-buffered, physiologic saline solution containing 0.3% lidocaine, similar to bovine collagen fillers. CosmoDerm 1 (approved in 2003), 35 mg/mL human collagen, and CosmoDerm 2 (approved in 2005), 65 mg/mL human collagen, are both similar to their bovine counterparts in indications and properties. CosmoPlast (approved in 2003), 35 mg/mL cross-linked human collagen, is similar to Zyplast (approved in 1985) in indications and properties. The CosmoDerm and CosmoPlast family of fillers was originally believed to have an extended clinical benefit compared to bovine collagen fillers,[2] but clinical practice has shown that the duration of clinical benefit is similar. The true benefit of human collagen fillers is that no skin testing is required.

As with any soft tissue augmentation agent, complications may occur; however, reported hypersensitivity with the CosmoDerm and CosmoPlast family of fillers has been limited primarily to a small degree of anticipated transient postprocedure swelling, bruising, and erythema. Until 2005, there were no reports of any hypersensitivity to this family of human collagen fillers.[15] Despite initial notions that human collagen cannot produce hypersensitivity, the rare isolated cases of hypersensitivity evidence its possibility and the need for aesthetic physicians to know of this potential, as well as effective treatment modalities.

CASE REPORTS

We present 2 patients who experienced hypersensitivity to human collagen fillers. The first was a 46-year-old

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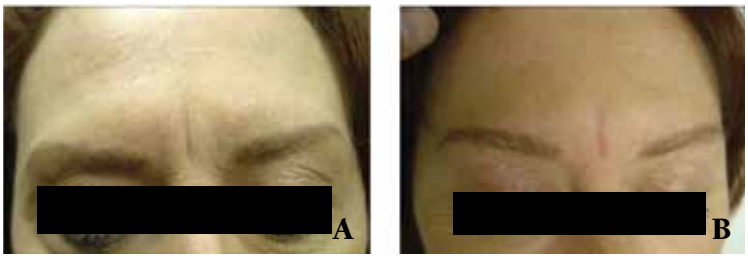

Figure 1. Patient before (A) and 6 weeks after (B) injections of CosmoDerm 1 into the glabellar furrow.

woman who, in August 2005, presented for CosmoDerm 1 injections into her glabellar furrow; she had no history of filler use and no medical history of autoimmune disease. Six weeks later, the patient presented with erythema over the injection areas that had developed over 10 to 14 days (Figure 1). The patient was initially treated with clocortolone pivalate 0.1% cream, a midpotency topical steroid, twice daily for 2 weeks, and then pimecrolimus 1% cream, a topical calcineurin inhibitor, twice daily for 3 weeks; however, there was no improvement. In October 2005, the patient was treated with the Palomar LuxG Pulsed Light Handpiece (32 J/cm^2/20 ms) for 2 pulses to the injection areas. She also continued on pimecrolimus 1% cream. There was still residual erythema at the injection areas 10 weeks after initial treatment, so she was again treated with the Palomar LuxG Pulsed Light Handpiece (36 J/cm^2/20 ms and 34 J/cm^2/20 ms) and continued on pimecrolimus 1% cream. Within another 2½ weeks, the erythema resolved completely, and no residual sensitivity was noted over the following 10 months.

The second patient was a 70-year-old woman who presented for injections with CosmoPlast. She had a history of filler use, including poly-L-lactic, hyaluronic acids, and Zyplast without complications, and had received silicone injections more than 25 years earlier. She had a history of numerous allergies, including foods such as shellfish and nuts and medications such as sulfa. She was injected with CosmoPlast in the marionette lines and vermilion border of the upper lip. She had no reaction to the injection until 14 days after treatment, when she reported pruritus at the injected areas. On examination a few days later, she showed erythema and edema at the injection areas. In addition, she presented with palpable, tender nodules in the vermilion border. She was treated with desoximetasone 0.05% cream twice daily (Figure 2). After 5 to 6 weeks, the erythema resolved without additional treatment.

COMMENT

Collagen fillers have remained a standard of therapy for rhytides and lip augmentation since their introduction. Compared with bovine collagen fillers, human collagen fillers offered the advantage of no required skin testing, allowing for immediate treatment. Human collagen, developed from purified fibroblast cell culture, is extensively tested before release in single-use sterile syringes. Thorough FDA testing of Zyderm, Zyplast, CosmoDerm, and CosmoPlast has revealed similar composition and purity of these fillers, allowing the expectation of similar clinical effect.[14]

Theoretically, because the filler is a human derivative, there should be complete homology and no risk of immunogenicity. However, as with any filler, additives are present, creating the potential for hypersensitivity. Both human and bovine collagen fillers are developed in phosphate-buffered, physiologic saline solution containing 0.3% lidocaine; the only difference is the source of the collagen.[7] In a CosmoDerm 1 clinical trial, 1 of 428 patients endured erythema, moderate pain, tenderness, induration, and swelling one week after the first intradermal injection into the volar forearm. The patient's symptoms resolved after 10 days without intervention. Histopathologic examination with a biopsy of the injection area revealed that the reaction was not immunologic; there was no antibody response against the filler.[14]

Two reports of more apparent hypersensitivity to human collagen fillers were reported by Stolman[15] in 2005. The first patient was a 53-year-old woman with no history of filler use and who had tested negative in a Zyderm skin test but did not proceed with bovine collagen filler injections. She was later treated with 1-mL injections of CosmoDerm into her nasolabial folds because of the recent availability of the filler on the market. Seventy-two hours after this treatment, the patient endured an

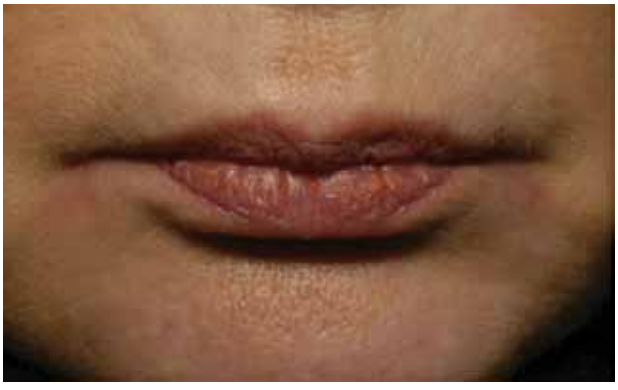

Figure 2. Patient who presented for CosmoPlast injections in the marionette lines and vermilion border of the upper lip. Photograph was taken following 1 week of treatment with desoximetasone 0.05% cream. Erythema was still present, and the patient complained of pruritus in the injection areas. Symptoms resolved completely after 5 to 6 weeks.

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Case Reports of Collagen Reactions

Author	Patient Age, y	Past Fillers Used	Filler Used	Reaction	Treatment
Cohen*	46	None	CosmoDerm 1	Erythema over treated areas for 6 wk	Clocortolone pivalate 0.1% cream: no improvement; pimecrolimus 1% cream: no improvement; Palomar LuxG Pulsed Light Handpiece and pimecrolimus 1% cream: resolution in 13 wk
Kaufman*	70	Hyaluronic acids; Zyplast; silicone; poly-L-lactic acid	CosmoPlast	Pruritus, erythema, edema, and nodules	Desoximetasone 0.05% cream: resolution in 5–6 wk
Stolman[15]	53	None	CosmoDerm	Erythematous, burning reaction	Tacrolimus 0.1% ointment twice daily for 3 wk
Stolman[15]	47	Zyplast	CosmoDerm	Erythematous and nonerythematous lumps	Tacrolimus 0.1% ointment for 6 wk

*Case reports presented in this article.

erythematous, burning reaction that gradually diminished with tacrolimus 0.1% ointment twice daily for 3 weeks (Table).

The second patient was a 47-year-old woman who had been treated with Zyplast. After this treatment, she reported lumps at the injection areas. The cause of the lumps was considered to be the technique, not the bovine collagen filler itself, and fortunately they resolved over 5 months without intervention. This patient was later treated with 1-mL injections of CosmoDerm into her perioral area. Because she was so pleased with the clinical effect, she received additional 1-mL injections of CosmoDerm 5 days later. Five days after the second treatment, she reported lumps similar to those she experienced from Zyplast, along with new erythematous lumps at the areas of recent injections. On examination, palpable perioral erythematous and nonerythematous subcutaneous lumps were noted and treated with tacrolimus 0.1% ointment twice daily. This treatment helped to resolve all the lesions over 6 weeks.

The developer of CosmoDerm declined to make available materials to test these 2 patients, so the cause of their hypersensitivity to human collagen fillers remains unknown.[15]

A shortcoming of these case reports is that biopsies of the injection areas were not obtained to confirm the presence of a true immunologic reaction. Although it is clear that hypersensitivity may occur with human collagen fillers, the reactions tend to be mild and short lived. It is important to present this information to patients before they receive treatment. With the unavailability of the fine-line hyaluronic acid products, as well as the Tyndall effect that may result from superficial placement of hyaluronic acid products, human collagen fillers such as CosmoDerm and CosmoPlast are still considered to be the gold standards of injectable filler therapy in the United States. Aesthetic physicians should know of the potential hypersensitivity from human collagen fillers, as well as effective treatment modalities for these reactions.

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