Severe Site Reaction After Injecting Hyaluronic Acid–Based Soft Tissue Filler

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Over the last decade, the soft tissue filler modality of cosmetic dermatology has undergone remarkable growth in the number of performed procedures, the types of available fillers, and the different brands marketing each type of filler. While the safety profiles of different fillers vary depending on the injected materials, overall fillers are considered relatively safe and are well tolerated. Common to different fillers are transient injection-site reactions, including tenderness, erythema, ecchymosis, and edema. This report describes the presentation and treatment of a severe site reaction in a patient treated with a hyaluronic acid–based filler also containing lidocaine. Culture and biopsy revealed a sterile, foreign body giant cell reaction. The patient was treated with systemic corticosteroids, numerous incision and drainage procedures, and hyaluronidase injections before adequate anatomic restoration was achieved.

The number of cosmetic procedures using soft tissue fillers has almost tripled over the last decade. About 1.6 million soft tissue filler procedures were performed in the United States in 2008.[1] Among the different filler materials, including calcium hydroxylapatite, nonhuman collagen, human collagen, fat, hyaluronic acid (HA), poly-L-lactic acid, and polymethylmethacrylate, more than 1 million procedures used HA as their filler of choice. Within each filler-type category the number of marketed brands also has grown substantially. For HA-based fillers, Restylane, Perlane, Juvéderm, Hylaform, Captique, Matridex, Prevelle Silk, and Hydrelle (formerly Elevess) are some of the available products. Hylaform is derived from rooster combs while the other HA filler products often are produced by and purified from the bacteria *Streptococcus equi* subsp *zooepidemicus*.[2]

With respect to the safety profile of dermal fillers, local injection-site reactions such as tenderness, erythema, ecchymosis, and edema, in addition to herpes reactivation and rarely vascular occlusion, are common to all dermal fillers. Nonhuman collagen fillers, bovine more than porcine, may generate hypersensitivity reactions, and hence, preemptive allergy testing is advisable. In contrast, human fibroblast-derived collagen fillers are much less prone to triggering hypersensitivity reactions.[3] Of note, Artefill, which contains polymethylmethacrylate, also contains bovine collagen and carries the risk for hypersensitivity reactions. Hyaluronic acid is believed to be notably less antigenic than

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collagen given its ubiquitous nature and the rooster comb–derived product, Hylaform is not associated with frequent hypersensitivity reactions.[4] Relative to Hylaform, bacteria-derived HA-based fillers Restylane and Perlane were found to have substantially more local injection-site reactions and hypersensitivity reactions.[5] Higher amount of injected protein, quicker swelling ability, and the use of a larger injection needle size for the larger particle size of Restylane and Perlane may be putative etiologies and/or confounding variables explaining this disparity.[6] Impurities remaining after purification of HA from bacterial broth also may account for the hypersensitivity reactions. The incidence of adverse events, including injection-site reactions and granulomatous reactions, declined from 0.15% in 1999 to 0.06% in 2000 after the introduction of more purified HA with notably decreased protein load; 6-fold less for Restylane.[7,8] The complication of granulomatous reactions also is germane to Juvéderm, another bacteria-derived HA filler product, whose Web site lists "lumps/bumps" as side effects.[9]

Since 2000, there have been a few published reports encompassing a total of 14 patients that have described the development of granulomatous reactions after nonanimal–based HA filler injections.[10-20] Out of these 11 publications of formation of granulomas after HA filler injection, 8 pertained to Restylane,[10-17] 1 to Matridex,[18] and another involving 2 patients that did not specify the source of injected HA.[19] The most recent report describes the development of granulomas in 3 patients after receiving Elevess (Anika Therapeutics, Inc.) injections.[20] Among the HA fillers, Elevess is unique in that it is the first one to be formulated with lidocaine 0.3%. It was approved by the US Food and Drug Administration (FDA) in 2006, was subsequently rebranded as Hydrelle in June 2009, and then marketed by Coapt Systems prior to Coapt System's recent bankruptcy filing.[21,22] Restylane, in comparison, was approved by the FDA in 2003 and has been approved in the European Union since 1996.[23] Both Elevess and Restylane are produced by *S equi*, and are indicated for moderate to severe facial wrinkles and folds. Elevess has a slightly higher concentration of HA than that found in Restylane (28 mg/mL vs 20 mg/mL, respectively).[2] Neither products' FDA approval letters list formation of granulomas as a potential side effect.[21,23] This report describes the development and treatment of a severe granulomatous reaction in a patient after receiving Elevess injections.

CASE REPORT

A 45-year-old female with no remarkable medical history and no known drug allergies was treated with Botox and Elevess in the same visit. She previously never received either product. Botox injections targeted the corrugator supercilii muscle, procerus muscle, midforehead, crow's feet, and lower eyelid. She then received 5 mL of Elevess to her bilateral nasolabial folds, upper and lower orbicularis oris muscles, philtral columns, marionette lines, glabellar and forehead creases, bilateral tear troughs, and dorsum nasi. For additional anesthesia, lidocaine cream 4%, 8 mL of lidocaine solution 1%, and 4 mL of marcaine solution 0.5% were used prior to injections of Botox and Elevess. Filler was injected into the deepest dermis and subcutis interface in a retrograde fashion. Patient tolerated the injections well with excellent cosmesis.

Three weeks after being injected, the patient noticed increasing diffuse swelling and itching on her forehead. An allergic reaction to HA was suspected, and oral methylprednisolone tapered dose pack and antihistamine therapy was initiated. She had substantial improvement in swelling, but the swelling recurred after finishing the steroid dose pack. The patient was afebrile and no signs of cellulitis, fluctuance, discharge, or development of nodules were appreciated. The patient was then started on 40 mg of prednisone taken orally once daily and referred to an allergist and to our office for a second opinion. In total she was evaluated by 3 allergists, all of whom discounted the possibility of an immediate onset, immunoglobulin E–mediated hypersensitivity reaction. One month after receiving the injection of Elevess, the patient had developed a leonine facies with diffuse edema of the forehead and midface region. On examination, multiple fluctuant and tender nodules were noted at injection sites, specifically on her glabella and midforehead and bilateral infraorbital and melolabial folds (Figures 1 and 2).

PATHOLOGY

A punch biopsy of a left buccal nodule was performed. The lowest magnification shows a dense granulomatous infiltrate that extends from the midreticular dermis deeper to the subcutis (Figure 3). A slightly higher magnification reveals that the granulomatous infiltrate surrounds pale staining deposits of foreign material (Figure 4). This foreign material is amorphous, nonpolarizable, and densely surrounded by multinucleated giant

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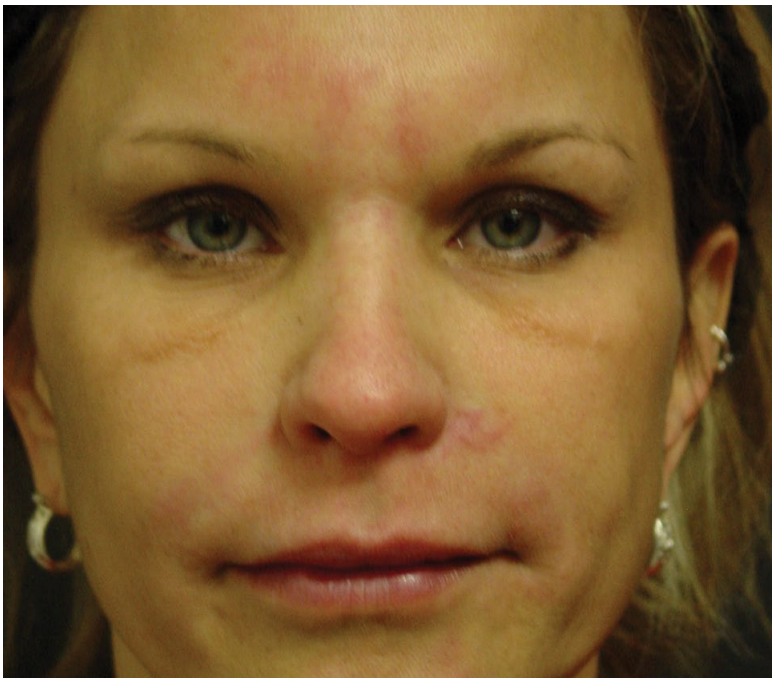

Figure 1. Forehead, glabellar, and melolabial erythematous nodules.

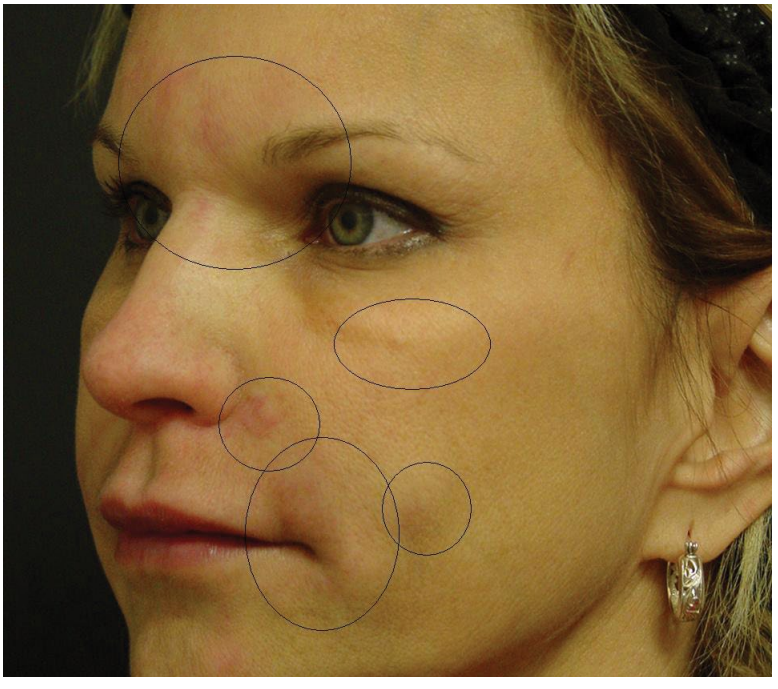

Figure 2. Lateral view photograph of patient at presentation with several nodules delineated, including infraorbital and buccal lesions.

cells in the absence of a dense lymphocytic or neutrophilic infiltrate (Figure 5). These histological findings were consistent with the pathological diagnosis of a foreign body giant cell reaction. Gomori methenamine-silver and periodic acid–Schiff stains were negative for fungi; Gram stain was negative for bacteria; Zeihl-Neelsen and Fite stains were negative for acid-fast organisms.

TREATMENT

Incision and drainage of 8 nodules was performed with expression of purulent discharge and samples were sent for Gram stain and aerobic, anaerobic, and mycobacterial cultures. Gram stain showed rare leukocytes but no bacteria, and all cultures were consistently negative for microorganisms. Four hundred units of hyaluronidase were injected into 8 nodules after drainage; however,

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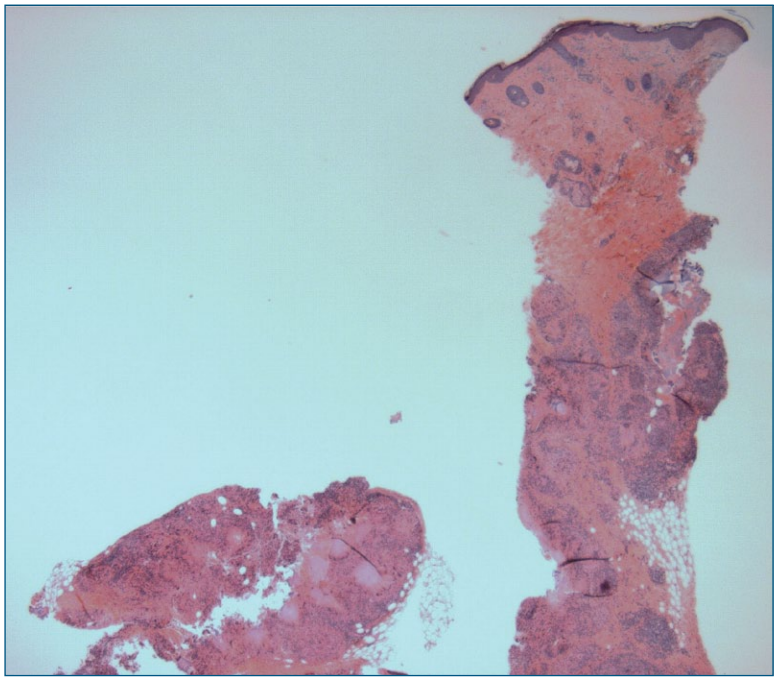

Figure 3. Punch biopsy of a left buccal nodule shows a dense granulomatous infiltrate extending from the midreticular dermis to the subcutis (H&E, original magnification ×2).

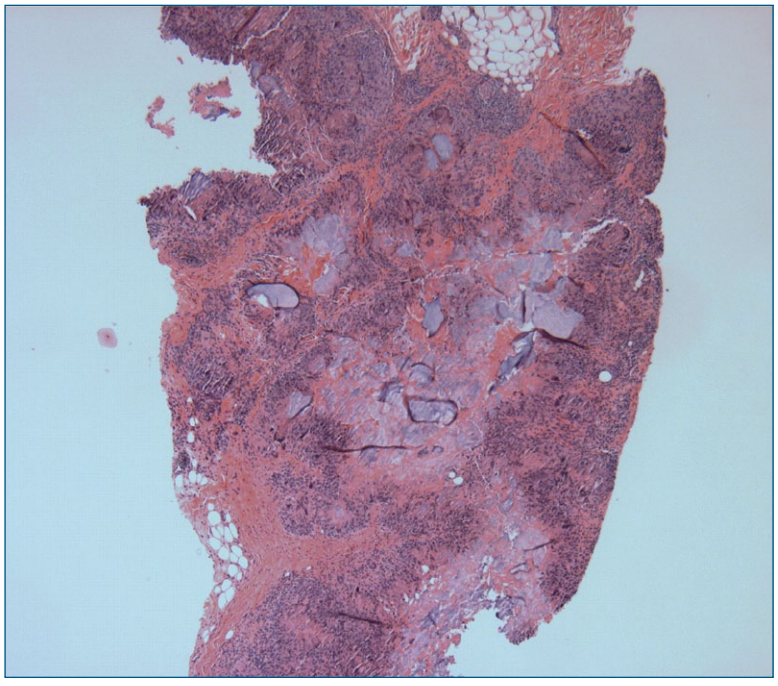

Figure 4. Punch biopsy of a left buccal nodule shows a granulomatous infiltrate surrounding pale staining deposits of foreign material (H&E, original magnification ×4).

likely given the severity of the inflammatory response and resultant edema, the hyaluronidase did not immediately dissolve the HA filler and collapse the tissue as expected from prior applications. Subsequently, the patient's 40 mg prednisone dose was tapered off. Incision, drainage, and hyaluronidase injection of these sites were repeated after 1 week. By this time, about 6 weeks after the initial injections of Elevess, the patient had considerable resolution of her swelling but still complained of itching.

Interestingly, another 6 weeks later the patient began complaining of tender, nodular swelling of her lower lip (Figure 6). These new nodules were treated with repeated incision and drainage procedures on 3 separate visits and a 1-week course of oral clindamycin 300 mg twice daily (Figure 7). Four months

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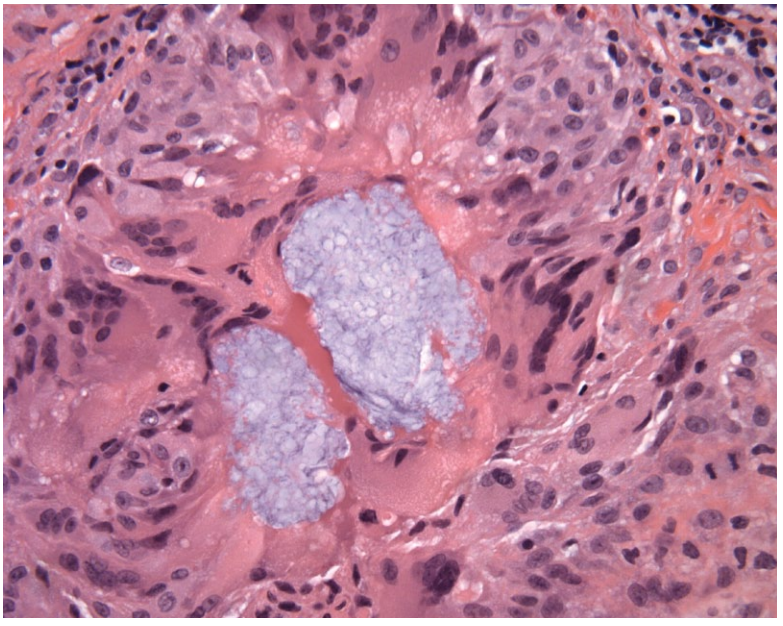

Figure 5. Punch biopsy of a left buccal nodule shows densely packed multinucleated giant cells surrounding 2 islands of amorphous material without a dense infiltrate of lymphocytes or neutrophils (H&E, original magnification ×40).

after the initial injections of Elevess, all of the patient's nodules had resolved and she returned to receive Botox treatment for her glabellar and forehead rhytides (Figure 8). To our knowledge, this patient was not treated with additional HA-based fillers after this unfortunate experience.

COMMENT

Dermal fillers are second only to botulinum injections in terms of the number of minimally invasive cosmetic procedures performed in the United States. Hyaluronic acid–based fillers enjoy the lion's share of this growing market. Specifically, the first approved HA-based filler, Restylane, has been widely used and studied extensively. While this type of filler enjoys a favorable safety-profile relative to hypersensitivity reaction–prone bovine and porcine collagen filler alternatives, it is noteworthy that adverse events extend beyond the ephemeral and self-limited injection-site erythema, tenderness, swelling, and ecchymosis. In addition to accidental vascular injection, occlusion, skin necrosis, and distant dissemination, granulomatous reactions are still a serious concern that patients must be informed of and that physicians must be able to diagnose and treat. This is in spite of the vast reduction in adverse events accomplished by decreasing the protein load in Restylane by 6-fold in 1999.[7,8] A review of the literature published after introduction of this safer formulation revealed 11 reports of granulomatous reactions post–HA-based filler injections.[10-20]

While 8 of these pertained to Restylane, one report of 3 patients developing granulomas after injections of Elevess raises questions about the safety of this relatively newly approved product, and merits further investigation as to their etiology.[20] The patient described above also developed the serious, relatively delayed complications of swelling and multiple tender, face-distorting nodules. These sterile nodules were histopathologically consistent with foreign body granulomas. While the etiological factors surrounding the development of granulomatous reactions after injecting a nonprotein, glycosaminoglycan-based substance like HA are unclear, there is apparent consensus on the treatment of this complication.[24] Antibiotics are indicated for nodules resulting after injections with HA-based fillers, especially if the nodules are tender. Incision, drainage, microbial cultures, and hyaluronidase injections are mainstays of treatment. The patient in this report was treated with oral corticosteroids without sustained improvement, and complete resolution was only obtained after repeated incision, drainage, and hyaluronidase injections. Antibiotics, specifically oral clindamycin, were used for painful lip nodules in addition to the procedures mentioned previously.

It is still unclear what causes these granulomatous reactions and how a patient's risk of developing this complication after injection with HA-based fillers can be mitigated. Biofilm formation, especially with longer-lasting fillers, and bacterial protein contaminants remaining after purification are 2 possibilities.[25] It also is not obvious whether the granuloma-causative factor is unique to Elevess relative to Restylane. While both fillers are produced by *S equi*, Elevess has a slightly

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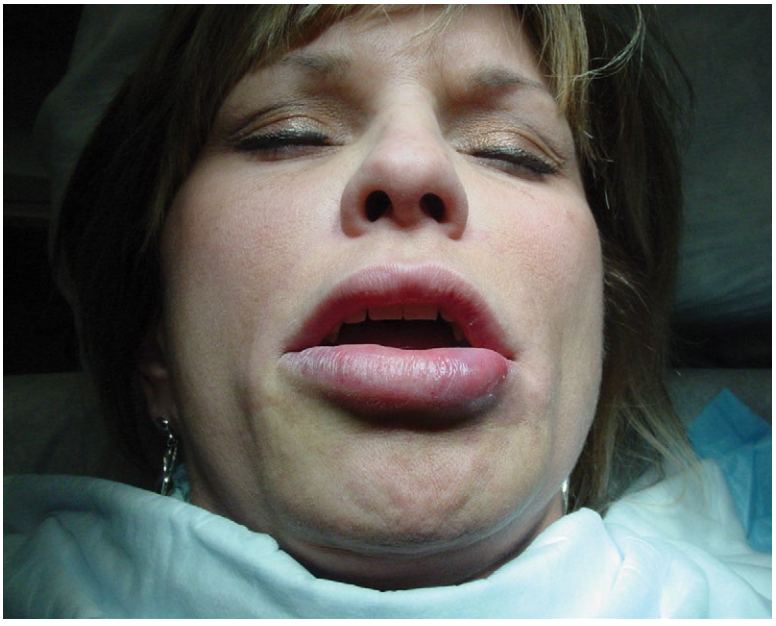

Figure 6. Nodular swelling of lower lip taken 12 weeks after receiving Elevess injections.

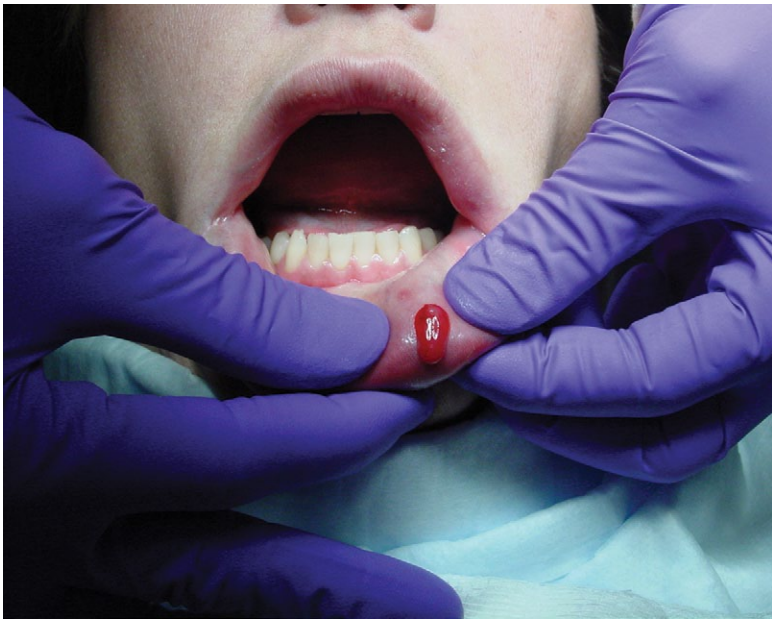

Figure 7. Patient's lower lip nodule at time of incision and drainage.

higher concentration of HA than Restylane, and this may translate into a higher bacterial protein load, perhaps similar to the pre-1999 formulation of Restylane.[2] Additionally Elevess uniquely contains sodium metabisulfite 0.1%, which may alter its immunoreactivity.

The development of serious adverse events after Elevess injections, in a time of transition for the product itself, reveals an important teaching point for regulators, physicians, and consumers. Despite being a fairly new entrant to the HA-based filler market, Elevess was rebranded as Hydrelle, and the company marketing the new brand, Coapt Systems, declared bankruptcy in July 2010.[26] It is unclear when, and if, a newly branded Elevess will be reintroduced and whether the known adverse events will be appropriately associated with the newly marketed product. The current scenario creates a vacuum for consumers and physicians in terms of product support. Safe usage of this filler product and others in a fast-changing product space necessitates a combination of full disclosure and extensive physician education. In addition, a mechanism for reporting adverse events is critical as part of a filler's postmarketing surveillance. A standardized, central information repository for all fillers,

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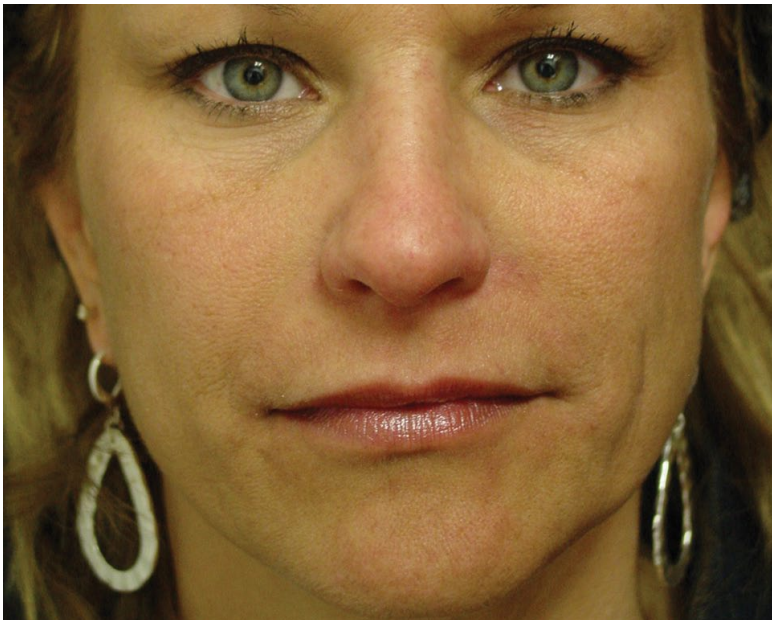

Figure 8. Patient 4 months after receiving Elevess injections showing resolution of the nodules after extensive treatment.

with detailed product composition and updated safety information, would help fill this unmet need. Such a resource would help physicians and patients make informed decisions when selecting a filler from a broader category, such as bacterially-derived HA-based fillers, that contains a plethora of products, and not decide solely on the basis of price or hearsay. With respect to Elevess, this report of multiple granulomatous formations adds to another recently published report[20] and merits further investigation as to its incidence, etiology, and prevention.

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