Adverse Reactions to Dermal Fillers: Review

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BACKGROUND. For many patients, injectable filling agents offer the promise of facial rejuvenation while offering reduced risks compared with more invasive surgery. With the increase in products available and the rise in the number of patients seeking this type of intervention, it is crucial that both the physician and the patient are fully cognizant of the risks involved with each product.

OBJECTIVE. To review the incidences and types of reaction to various commonly used injectable products.

METHODS. A literature review and personal experiences (gained largely in Europe over the past 8 years) of dermal fillers from 1996 to the present, including illustrative case reviews.

RESULTS. Reactions can be attributed to the procedure itself, the procedural technique, and the agent injected. Some of these reactions are preventable, whereas others are inevitable; most are mild and transient. Improving product formulations, altering the concentration of product injected, or changing the injection technique can dramatically reduce the incidence of adverse reactions. Since its reformulation in mid-1999, the biologically engineered hyaluronic acid filler Restylane (Medicis Pharmaceuticals, Scottsdale, AZ, USA) elicits less than one allergic reaction in 1,600 treatments. Skin reactions with poly-L-lactic acid (New-Fill/Sculptra, Dermik Laboratories, Berwyn, PA, USA) are considerably less likely if a greater dilution and deeper injection technique are employed.

CONCLUSION. Different injectable products have highly divergent properties, associated risks, and injection requirements. The dermasurgeon should be suitably experienced to select and use these products correctly.

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THE QUEST for and maintenance of a youthful visage are well established. Youth equates with vitality, fecundity, and attractiveness; disguising the passage of time etched in the face is not a new phenomenon, although the proportion of people living to old age is. Indeed, recent estimates suggest that the number of persons aged 65 years or older in the United States is expected to increase from 12.4% of the total population in 2000 to 19.6% in 2030.[1] Linking this demographic trend to rising expectations of antiaging therapies are advances in medicine and technology. Including over-the-counter face creams, laser surgery, chemical peels, injected products, and surgical face-lifts, innovative treatments can now make a substantial difference to an individual's appearance and are frequently used in combination to rejuvenate the aging face.[2]

Financial issues aside, the extent to which patients wish to alter their appearance largely drives treatment choice. Each option differs in the extent to which it can modify the appearance and the durability of achievable results. Injected products offer the consumer more dramatic results than facial creams and chemical peels yet are less invasive and can be more subtle than facial surgery. Within the class of injectable cosmetic products, some are more suited to the correction of fine lines (such as Zyderm I (INAMED Aesthetics, Santa Barbara, CA, USA), Cosmo-Derm (INAMED Aesthetics), Fine Hylaform (Inamed Corp), Restylane Thin (Medicis Pharmaceuticals, Scottsdale, AZ, USA), some are more appropriate for deeper lines and wrinkles (such as more robust hyaluronic acid derivatives, such as Hylaform Plus (INAMED Aesthetics), Restylane, Restylane Perlane (Medicis Pharmaceuticals /Q-Med, Uppsala, Sweden), and poly-L-lactic acid (PLLA; [New-Fill/Sculptra]), and some are able to improve facial lipoatrophy (such as PLLA). In addition, different products vary greatly in terms of durability and associated mechanisms of action (Table 1). They also differ in their propensity to elicit adverse reactions.

The occurrence of adverse reactions relates to both the inherent properties of the product and to inappropriate delivery or dilution of the filler, which may lead to harmful sequelae.[2–5] Although injectable substances are subject to approval by the US Food and Drug Administration (FDA), most are classified as class III devices. Some such products have been proven safe and effective for their indicated use, but there are few safeguards to prevent incorrect

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Table 1. Comparison of Injectable Dermal Implants

Product	*Duration of Correction**	*Mechanism of Action*
Biodegradable fillers		
CosmoDerm and Zyderm I and II (INAMED Aesthetics, Santa Barbara, CA, USA)	2–5 mo	Direct tissue augmentation with material injected
CosmoPlast and Zyplast (INAMED Aesthetics)	3–5 mo	Direct tissue augmentation with material injected
Hylaform Fine (INAMED Aesthetics)	2–3 mo	Direct tissue augmentation with volume
Hylaform Regular (INAMED Aesthetics)	3–6 mo	Direct tissue augmentation with volume
Hylaform Thick (INAMED Aesthetics)	4–6 mo	Direct tissue augmentation with volume
Hyalite (Mentor Corp, Santa Barbara, CA, USA)	Up to 9 mo (trials pending)	Direct tissue augmentation with volume
Hydrafill 1 (Corneal Group, Annecy, France)	3–4 mo	Direct tissue augmentation with volume
Hydrafill 2 (Corneal)	4–6 mo	Direct tissue augmentation with volume
Hydrafill 3 (Corneal)	9–12 mo	Direct tissue augmentation with volume
New-Fill/Sculptra (Dermik, Berwyn, PA, USA)	1–2 yr (perhaps longer) (trials pending)	Stimulation of collagen and other connective tissue synthesis
Restylane (Medicis Aesthetics Holdings Inc., Scotsdale, AZ, USA)	6–8 mo	Direct tissue filling augmentation with volume
Restylane Fine Lines, Touch (Medicis)	3–6 mo	Direct tissue filling
Restylane Perlane (Medicis)	9–18 mo	Direct tissue augmentation with material injected
Restylane SubQ (Medicis)	Several years (trials pending)	Deep tissue (cheek, malar) augmentation, chin augmentation
Nonbiodegradable fillers		
Artecoll/Artefill (Artes Medical Inc, San Diego, CA, USA)	Years	Encapsulation of PMMA spheres by collagen
Dermalive (Dermatech, Paris, France)	Years	PMMA microspheres in a suspension of hyaluronic acid
Radiance (BioForm Inc, Franksville, WI, USA)	Months to years (trials pending)	Stimulation of innate connective tissue using hydroxyapatite injection that forms scaffolding
Silicone	Years, possibly permanent	Replacement with volume injected as well as encapsulation of material by ingrowth of native connective tissue

PMMA = polymethylmethacrylate.
*From the literature, anecdotal reports, and personal experience.

use. Thorough training of specialist physicians (dermasurgeons), including appropriate product selection, preparation, and injection techniques, is required to minimize avoidable adverse tissue responses.

This article provides an overview of the tissue reactions resulting from injectable "filler" products.

Evaluating Adverse Reactions

Most adverse reactions are mild and transient; however, responses of greater significance can occur, demanding anything from a short course of medication to surgery. By definition, patients undergo intervention to improve some aspect of their appearance; therefore, any risk of disfigurement from a filler is unacceptable.[2]

Tissue reactions may occur because of the nature of the filler, even if the procedure is executed correctly, whereas some arise because of poor procedural technique. For example, the depth to which a product is injected is important for a variety of fillers (eg, too superficial placement of the hyaluronic acid fillers can lead to visible, pale nodules in the skin). Other reactions are dependent on the concentration of the product used, as has been observed in the case of injecting PLLA (N. J. Lowe, C. A. Maxwell, personal observations, 2002–2005). Moreover, some products may induce adverse events because of their inherent properties, such as their ability to elicit hypersensitivity reactions. Some reactions occur immediately after treatment, whereas some have a delayed onset, as summarized in Table 2. In summary, adverse reactions can be evaluated in terms of the following:

- Clinical seriousness
- Esthetic relevance
- Immediate versus delayed onset
- Causality:
  - Expected procedure-related events
  - Events related to improper technique
  - Reactions to the product

Table 2. Onset of Adverse Events

Early (occurring up to several days post-treatment)	*Delayed (occurring from weeks to years post-treatment)*
Injection site reactions	Infection (atypical, eg, mycobacterial)
Erythema	Erythema
Edema	Edema
Pain/tenderness	Pain/tenderness
Bruising	Nodule
Itching	Systemic responses to infection
Infection	Granulomatous inflammation
Erythema	Varying from subclinical histologic changes to disfiguring nodules
Edema	
Pain/tenderness	
Acne papule formation	
Nodule	
Hypersensitivity	Migration of implants
Erythema	
Edema	
Pain/tenderness	
Nonfluctuant nodules	
Lumps caused by maldistribution	Hypersensitivity
	Aseptic abscess
Discoloration	Persistent discoloration
Redness	
Whiteness	
Hyperpigmentation	
Local tissue necrosis caused by vascular occlusion	Persistent scarring

Skin Fillers

Reactions by Type and Time of Onset

Early Injection-Related Events

With all injectable products, the injection itself can cause a tissue response. The intensity of this inflammatory process is usually in proportion to the degree of tissue injury.[6] The inflammatory process is characterized by vasodilation of the local blood vessels with consequent excess local blood flow; increased permeability of the capillaries with the leakage of fluid into the interstitial spaces; clotting of the fluid in the interstitial spaces from excessive amounts of fibrinogen and other proteins leaking from the capillaries; migration of granulocytes and monocytes; and swelling of the local tissue.[6]

With some injectable products (such as Zyderm/Zyplast,[3] CosmoDerm, CosmoPlast (INAMED Aesthetics), Artecoll (Artes Medical Inc, San Diego, CA, USA), Hylaform, and Restylane), this process manifests itself as temporary swelling and/or erythema, which generally resolves within a day.[7] Bruising is inevitably more frequent in patients taking aspirin or other nonsteroidal anti-inflammatory agents within 4 days prior to injection. When the inflammatory response is more persistent or painful, the event should be classed as an adverse effect, although no clear line appears to exist separating expected injection-site reactions and reported adverse effects. Nevertheless, the rate of injection-site reactions classified as side effects has been reported for a number of injected products.[7] Such inflammatory reactions are to be expected, the probability of which depends on the product used. In general, less durable products, such as Zyplast or Hylaform, are less likely to cause early erythema than longer-lasting products, such as Restylane/Perlane. However, it has been our experience that some patients are willing to use temporary camouflage makeup in exchange for longer-lasting results.

A survey of approximately 7,000 patients who demonstrated a negative test result to bovine collagen revealed a side-effect rate at the injection site of 1.5%, the symptoms of which were mostly limited to erythema, induration, itching, and pain.[8] Similar tissue responses have been reported to occur with a product derived from cadaveric human tissue (Cymetra, LifeCell Corporation, Branchburg, NJ, USA). As with bovine-derived collagen, adverse reactions (which occur at a rate of 2.1%) included bruising, redness, and swelling, all of which were reported to be transient.[7]

A relatively new injectable product uses partly denatured 3.5% bovine collagen as a carrier substance for small spheres of polymethylmethacrylate (PMMA) (Artecoll/Artefill). Injection stimulates tissue fibroblasts to produce the patient's collagen, which encapsulates the PMMA spheres.[7] As with other injected products, acute postinjection swelling occurred and usually lasted approximately 1 day, although bruising occurred in about 20% of patients undergoing lip augmentation.[7]

Hyaluronic acid fillers have become widely used in Europe over the last 8 years[2] and are also becoming increasingly available in North America.[9] Some products (such as Hylaform and Restylane) are produced by introducing sulfonyl-bis-ethyl crosslinks between the hydroxyl groups of the polysaccharide chain of hyaluronic acid.[7] Hylaform, derived from rooster combs, is also associated with transient and mild erythema, itching, swelling, and pain. Related reactions, including more persistent erythema, acne papule formation, and ecchymotic changes, have been noted in approximately 2% of treatments, but all resolved without sequelae.[2,6,7] Restylane—a non–animal-stabilized hyaluronic acid gel—is manufactured from a process involving the fermentation of specific strains of streptococci. A retrospective review of adverse event data from Europe, Canada, Australia, South America, and Asia with this product indicated that there were 68 cases of injection-site inflammation (0.05%) in 1999. Symptoms again included redness, edema, and tenderness shortly after injection, which were reported to be mild to moderate and self-limiting, with an average duration of 4 days.[10]

Poly-L-lactic acid (New-Fill or Sculptra in the United States), recently recommended for approval by the FDA Advisory Committee for the correction of human immunodeficiency virus (HIV)-related facial lipoatrophy, has been used in Europe for approximately 3 years for both correction of HIV-related lipoatrophy[11] and cosmetic rejuvenation of non-HIV patients. With this product, temporary edema and bruising occurred in a minority of patients (10% of 500 patient treatments) (N. J. Lowe and C. A. Maxwell, unpublished data, 2002–2005).

Immediate and early tissue responses to injected products are to be expected. Therefore, patients should be warned that these responses might occur but equally be reassured that they are mild and transient. Indeed, it is our experience that effective camouflage makeup can conceal early reactions, although bruising is more difficult to mask effectively.[2]

Skin Discolorations

With all injected products, skin discoloration of esthetic significance can occur at the site of treatment; such reactions typically occur immediately after injection and generally resolve within a few weeks.[12] Redness occurs as a result of the inflammatory response, whereas whiteness at the injection site can be attributed to overcorrection and the color of the injected substance.[2,3] Hyperpigmentation (which can be treated with depigmentary cream) and bluish discoloration have also been reported, particularly in cases of products containing hyaluronic acid. The bluish discoloration may represent both traces of hemosiderin associated with vascular injury[13] and visual distortion from light refraction to the filler through the skin (Tyndall effect). Product-specific training and rigorous adherence to the manufacturer's instructions should minimize the risk of discoloration occurring (eg, correct depth of injection).

Immediate Hypersensitivity Reactions

Some individuals may develop allergic reactions to injected products: hypersensitivity reactions represent a state of altered reactivity in which the body responds with an exaggerated immune response to a foreign substance. Such reactions generally occur within minutes of exposure to a challenging antigen owing to the release of histamine, which causes vascular permeability, edema, erythema, pain, and itching. Hypersensitivity skin reactions to cosmetic products can be severe, and cases of severe anaphylactic shock have occasionally been reported.[14] The occurrence is very rare; one report documents only two patients with allergy to ocular placed bovine collagen.[13] Clearly, some substances are more likely to elicit a hypersensitivity reaction than others; autologous tissue does not cause an allergic response, whereas those containing local anesthetic may be expected to show a greater incidence.

Delayed Hypersensitivity Reactions

Correct patient screening and testing are of great importance in bovine collagen therapy.[3] Fortunately, potential allergenicity to injectable collagen is reliably determined by skin testing. A positive skin test (seen in 3.0 to 3.5% of patients), characterized by a change in the contour of the injected implant, erythema, edema, itching, and, occasionally, an indurated papule or inflamed dermal nodule, is a definite contraindication to treatment.[3,12] Since 1 to 3% of patients with one negative skin test subsequently develop a reaction at the treatment site, double skin testing is advocated.[3,14]

Similarly, because PMMA spheres in Artecoll are carried in partially denatured bovine collagen, it also poses an allergic risk. Although no skin test is currently required prior to PMMA injection, the reported allergy rate with the treatment is 0.78%.[7] In light of this, we feel that skin testing prior to injection with PMMA is desirable. Hyaluronic acid–based products have also been associated with allergic reactions, prompting some discussion of skin testing with these agents.[15] For example, Lowe and colleagues reported delayed hypersensitivity skin reactions to hyaluronic acid derivatives in Hylaform and a past formulation of Restylane in 0.42% of 709 patients treated between 1996 and 2000, likely as a result of a variety of ingredients in the products.[15] One of the authors (N.J.L.) has seen one patient who developed a mild delayed erythematous reaction to CosmoPlast 6 weeks postinjection who had a positive forearm test response, again appearing after 6 weeks. She had a previous Zyplast skin reaction. This resolved without sequelae (Figure 1).

Refinement of some specific products, such as Restylane and Perlane, in mid-1999 has resulted in a notable reduction in delayed adverse reactions. For example, one retrospective study of patients treated with these non–animal-stabilized hyaluronic acid gels reported a 50% reduction in delayed hypersensitivity reactions in 2000 compared with 1999, most likely attributable to improvements in the manufacturing process.[10] Reinforcing these results, a retrospective analysis of over 1,600 patient treatments showed no case of delayed allergic reactions to the more purified versions of Restylane and Perlane, illustrating how small variations in product formulations can have a significant impact on adverse reactions (N. J. Lowe, unpublished data, 2000–2005) (Figure 2).[2] These improvements convince us that skin testing for Restylane/Perlane is not required.

Late Adverse Reactions

Nodule Formation

Nodules, which can arise from a number of causes, are not uncommon following soft tissue augmentation; therefore, investigations may be required to establish a diagnosis. Nonerythematous nodules can form immediately after injection as a result of the uneven distribution of product.[2,15] Such nodules are distinct from the inflammatory responses that are to be expected early following injection, whether as

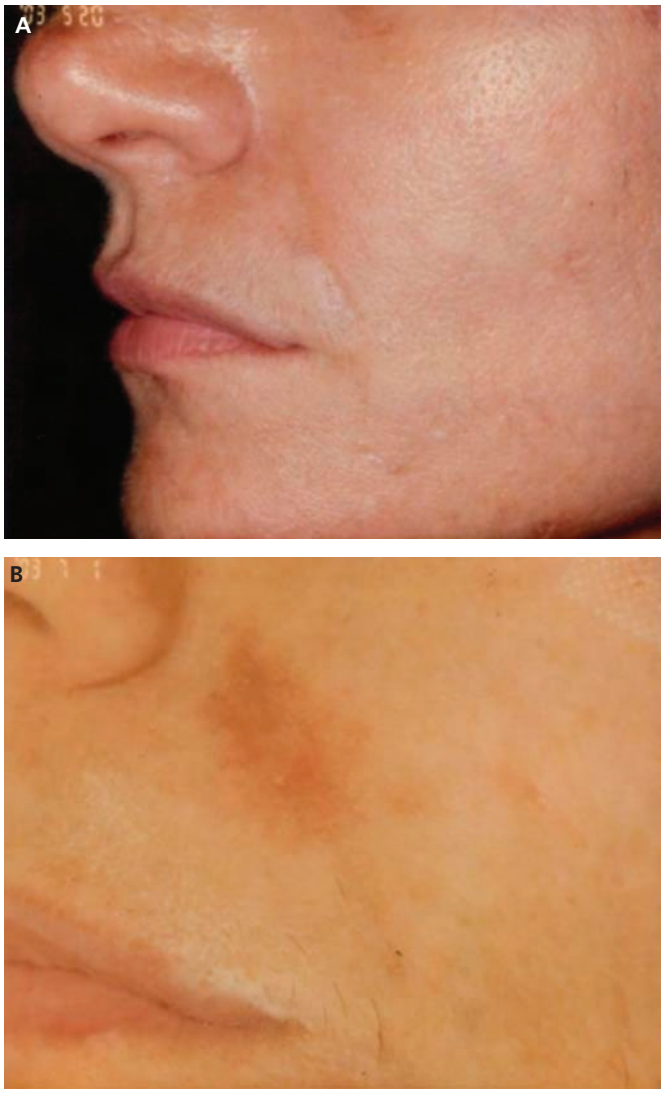

Figure 1. CosmoPlast: immediate correction (A); delayed allergic reaction, 6 weeks postinjection (B). The patient had a previous delayed allergy to Zyplast.

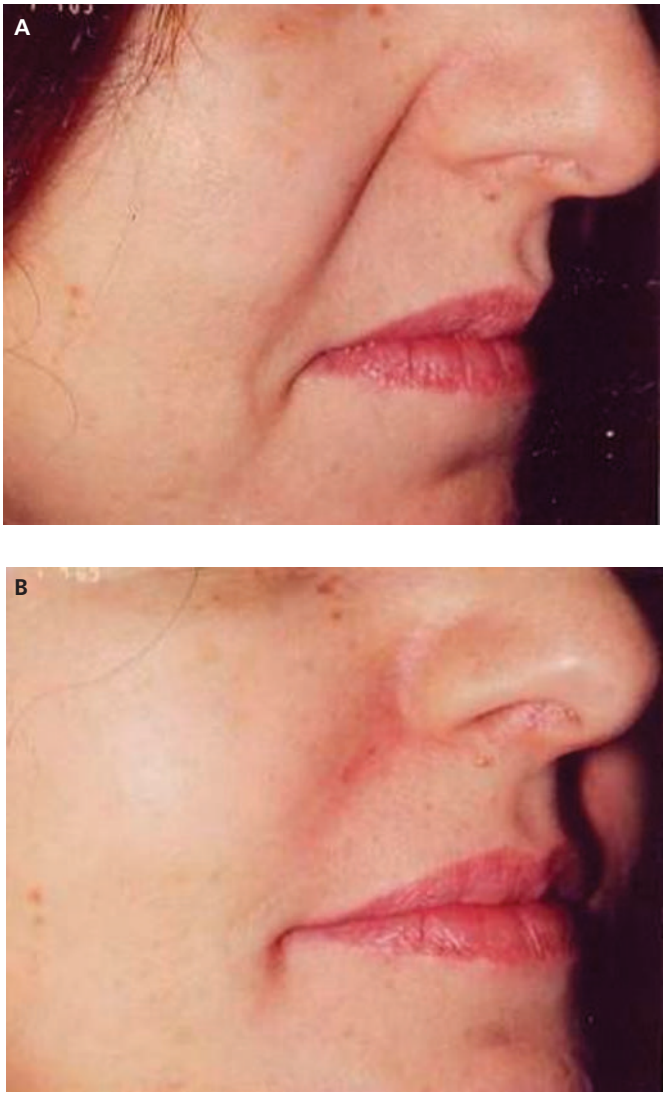

Figure 2. Nasolabial folds and lip augmentation before (A) and after (B) Perlane.

a reaction to injury (which should disappear within days) or infection. Clinical presentation of infection can include single or multiple nodules with inflammatory signs. Nodules may present subcutaneously or in the dermis and may or may not be painful.[16] In addition, treatment-associated hypersensitivity can lead to nodules that are usually inflammatory.[10,16] If symptoms persist, a diagnosis should be sought to confirm and treat infection or establish a diagnosis of hypersensitivity through skin testing (Figures 3 and 4).

In some cases, nodules occur that are of neither clinical nor esthetic significance and, therefore, do not warrant histologic examination. For example, a recent open-label, single-arm, pilot study evaluated the efficacy and safety of facial injections of PLLA in HIV-infected patients with severe facial lipoatrophy. Palpable but nonvisible and nonbothersome subcutaneous "micronodules" were not uncommon (44% of patients), but by the end of the 96-week study period, spontaneous resolution was observed in 27% of affected patients.[17] In contrast, Lowe and Maxwell reviewed 200 patient treatments with PLLA diluted in 4 cc of sterile water and 1% lidocaine. With this dilution and with subcutaneous injection, subcutaneous nodules were relatively rare (< 5%). They were also self-limiting and resolved within a few weeks, rarely requiring intralesional corticosteroid injection (N. J. Lowe and C. A. Maxwell, unpublished data 2000–2005) (Figures 5 and 6).

Such nodules may be transient inflammatory granulomatous reactions (see below), although some have suggested that they are the result of the development of a fibrous reaction as a response to the presence of the implant. The process of neocollagenesis persists despite the resorption of the PLLA particles and is one putative

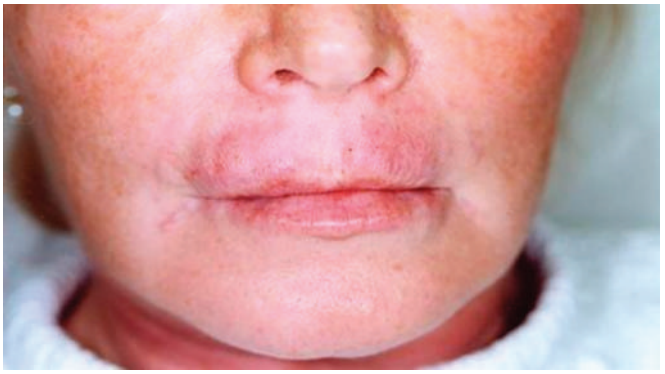

Figure 3. Delayed nodular erythematous allergic reactions to Hylaform 8 weeks postinjection.[15]

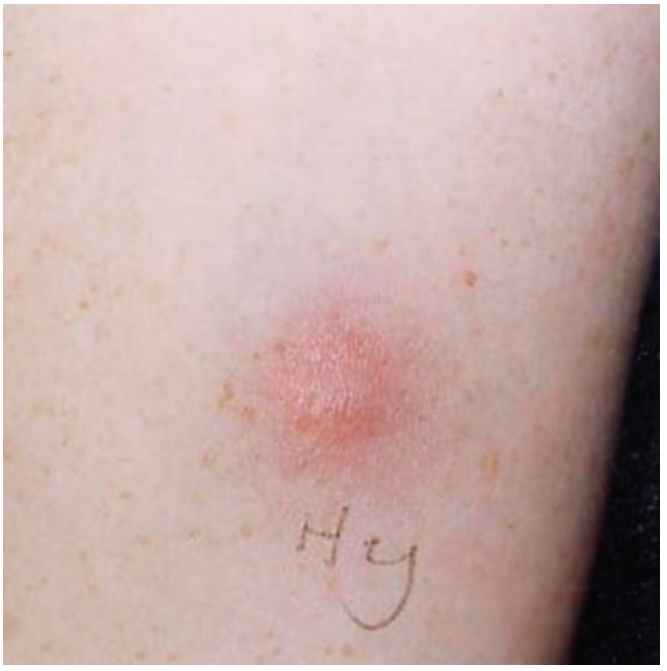

Figure 4. Forearm 8 weeks after skin test with Hylaform.

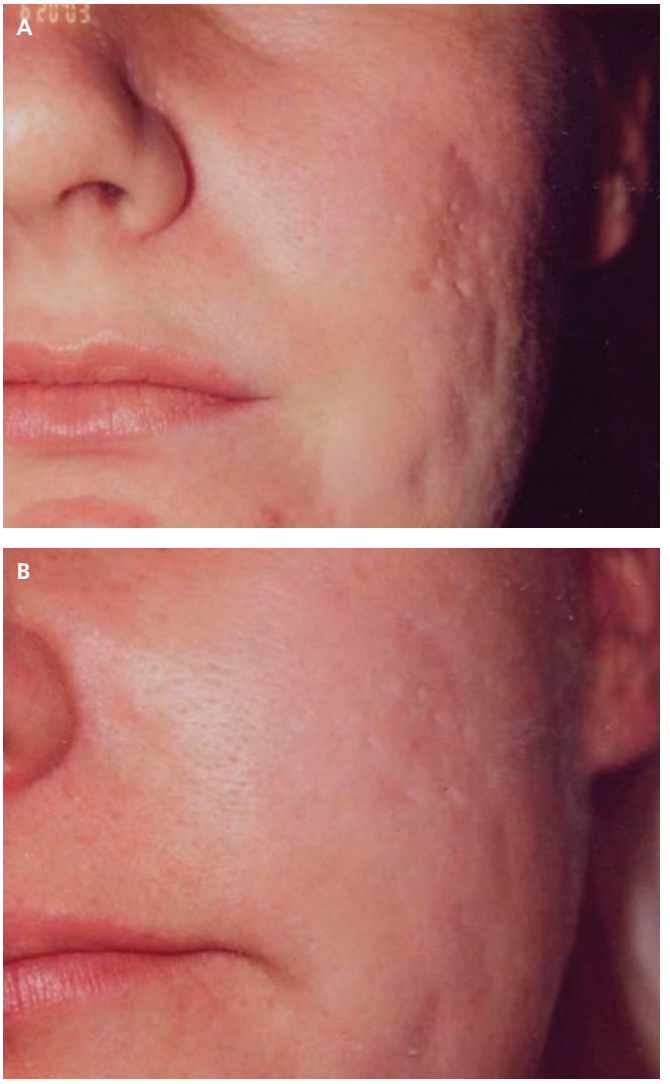

Figure 5. Atrophic acne scars before (A) and after (B) three New-Fill treatments.

mechanism by which PLLA adds volume to recontour the face.[11] The morphology of the injected microspheres suggests that the process of neocollagenesis initially occurs in niduses that give rise to the observed micronodules.

Foreign Body Granulomatous Inflammation

In addition to infection, inflammation, maldistribution of the product, hypersensitivity, and the process of neocollagenesis, foreign body reactions can occasionally precipitate the appearance of lumps and bumps by leading to granulomatous inflammation. However, without histologic examination, a definite diagnosis of granuloma is impossible.

Histology

Granulomatous inflammation is a histologically distinctive form of chronic inflammation that occurs in particular circumstances in response to certain organisms or foreign material. As part of the latter category, biomaterials implanted in soft tissue evoke, with few exceptions, foreign body granulomatous inflammation.[18] The function of such reactions is to isolate and prevent the migration of bodies that cannot immediately be removed by enzymatic breakdown or phagocytosis.[6] Visible, clinically significant granulomas represent an extreme and rare manifestation of granulomatous inflammation.[18,19] Irrespective of the severity of inflammation, histologic examination is required to diagnose this form of tissue response.

Granulomas can be characterized as aggregates of particular types of chronic inflammatory cells that form nodules, normally of a few millimeters in diameter, although larger areas can by formed by several granulomas merging. What distinguishes granulomas from other components of the inflammatory response is the collection of modified

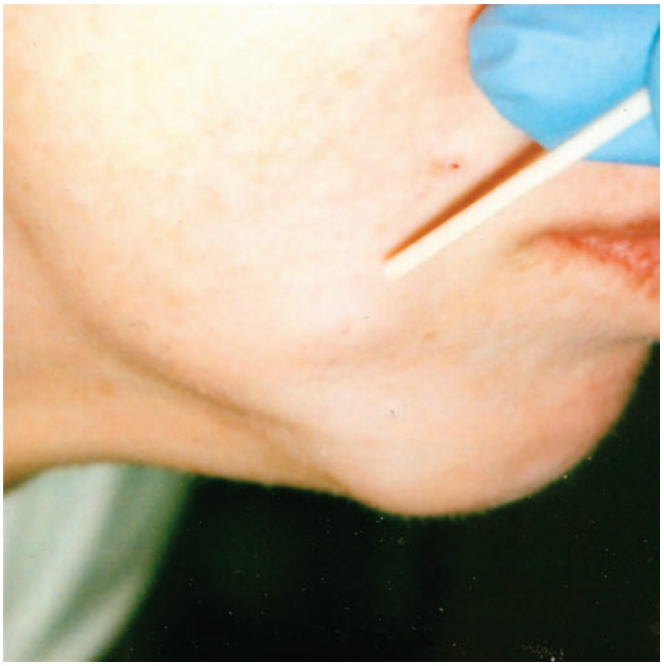

Figure 6. A subcutaneous nodule from New-Fill (Sculptra) observed during a course of injections 12 weeks following the first 6 weeks after the second injection. Successfully treated with intralesional triamcinolone injections.

macrophages, epithelioid cells. The function of epithelioid cells remains unclear, but it appears that such cells are less phagocytic than other macrophages and are modified for secretory purposes. These epithelioid cells are usually surrounded by lymphocytes.[19]

Macrophages in granulomas are commonly further modified to form multinucleate giant cells. These arise by the fusion of epithelioid macrophages without nuclear or cellular division, thus forming huge single cells, which may contain dozens of nuclei. In giant cells characteristic of foreign body reactions, the nuclei are randomly scattered throughout the cytoplasm (whereas in the case of granulomas seen with tuberculosis, for example, the nuclei are arranged around the periphery of the cell [Langerhans-type giant cell]).[19–21]

Histologically, the severity of foreign body granulomatous inflammation can be classified in terms of the types and number of cells present. For example, Duranti and colleagues proposed a classification of foreign body reactions based on the extent of granulomatous inflammation[22]:

- Grade 1: slight inflammatory reaction with a few inflammatory cells (predominantly macrophages, lymphocytes, and plasma cells, with neutrophil and eosinophil polymorphonuclear leukocytes as possible minor components; this is distinct from acute inflammation, in which neutrophils predominate)
- Grade II: clear inflammatory reaction with one or two multinucleate giant cells
- Grade III: more giant cells, the presence of lymphocytes, and fibrous tissue with inflammatory cells
- Grade IV: granuloma with encapsulated implants and a clear foreign body reaction

This histologic classification was recently used by Lemperle and colleagues to characterize a number of responses to injectable substances for soft tissue augmentation.[23] Ten commercially available substances were evaluated for biocompatibility and durability by injecting the agents into the volar forearm, followed by excision and histologic examination of the sites at 1, 3, 6, and 9 months. All substances exhibited some degree of foreign body inflammation at the outset but were pronounced to be clinically and histologically safe.[23] However, since the mechanism of actual granuloma formation is still unknown, such findings cannot predict future reactions.

Clinical Significance of Granulomatous Inflammation

Given that subclinical granulomatous inflammation is a normal tissue response to injected materials, the clinical significance of granulomatous inflammation should be based on the extent, severity, and long-term progression of the response. Patients with granulomas usually present with nonfluctuant lumps felt under the skin, in contrast to infectious lesions, which are normally fluctuant and erythematous. However, in the absence of obvious signs of infection (fever, leukocytosis, malaise, suppurative or purulent exudates), histologic and/or microbiologic examination is required to confirm the presence of granuloma and/or diagnose infection.

If present, histologic examination cannot only confirm granuloma, it can also potentially point to the type of implant that caused the foreign body reaction. The configuration of the cystic spaces associated with the granuloma has the potential to differentiate the type of product injected because the size and shape of the particulate can dictate cellular structure.[21]

The rate of clinically detectable granuloma formation is reported to vary between 0.01 and 0.1% with injected products such as collagen,[23] hyaluronic acid,[15] and particulate injectables.[15,20,24,25] Granulomas occur less frequently after injection of resorbable implants compared with more permanent products. The risk of granuloma is said to be reduced following the implantation of products containing microspheres with smooth surfaces, such as PMMA, compared with particles with irregular surfaces.[22]

Treatment of Granulomas

Clinically significant granuloma can be treated successfully by the administration of local or systemic corticosteroids, although the therapeutic role of these agents in the treatment of cosmetic orofacial granulomas has yet to be extensively studied.[26] Prednisone is most usually used in doses up to 60 mg/d, with resulting improvement in patient signs

and symptoms. Senet and colleagues also reported successful treatment response with the use of minocycline for the treatment of two cases of cutaneous silicone granuloma.[27,28] The beneficial effects of minocycline are thought to be related to the agent's anti-inflammatory, immunomodulating, and antigranulomatous properties, which have previously been demonstrated in vitro.[27] Another approach is to discourage aberrant cell growth by injecting 5-fluorouracil plus corticosteroids and, in the event of failure, to administer oral hydroxychloroquinine hydrochloride.[12,28]

For well-circumscribed nodular lesions, surgical excision is a very effective approach to eradication. However, where lesions are widespread, surgery may lead to scarring and fistulae.[26] Several such cases of very severe granulomatous reactions have been reported in the literature. For example, Maas and colleagues reported a retrospective review of seven cases with severe complications from cosmetic procedures. All patients required surgery; three of the seven required débridement and resection extensive enough to warrant flap reconstruction.[19] Alarmingly, these reactions presented years after the cosmetic procedure, at which point, several patients could not recall the name of the product with which they had been treated. Moreover, these reactions were reported in concert with questionably trained individuals using questionable methods.[19,29]

The delayed appearance of such reactions appears to be a particular feature of injected silicone, which has been used extensively in some countries for decades.[26]

At least nine reports of granulomatous inflammation after facial silicone injection exist; the time interval between the injection and onset of symptoms ranges between 5 months and 15 years.[26] It would appear that the permanence of the product allows for a greater length of time for severe foreign body reactions to occur. It is suggested that microdroplet injection with silicone reduces nodular granulomas and migration of injected product.

Other Adverse Events

Migration of Fillers

Unique among the injectable products available for soft tissue augmentation, silicone has the ability to migrate to locations distant from the original treatment site. The pattern of clinical presentation can be similar to malignant neoplasm or granulomatous diseases, and the spread of silicone has been reported to many organs[26]; whether this occurs with medical-grade silicone and the true microdroplet technique is not clear. This can be uncomfortable and worrisome for the patient and may even lead to the initiation of unnecessary treatment. Silicone injections offer long-term correction but at the price of long-term complications; patients should be warned of the possibility of migration and the appearance, years after implant, of severe granulomatous reactions. However, some feel that microdroplet injection of unadulterated medical-grade silicone has minimal risk of side effects.

Adverse Events Related to Improper Technique

Infection

Since the skin is traumatized in all facial augmentation procedures, injected dermal products and cosmetic surgery can be associated with infection. Moreover, the growing population of untrained and unlicensed personnel performing procedures in nonmedical settings clearly places the patient at unnecessary risk of infection.[30,31]

A distinction, based on clinical seriousness, can be made between early and late postprocedure inflammation and infection. In the case of early infection, the resultant lesions are virtually indistinguishable from the inflammatory response described above and either resolve spontaneously or require minimal medical intervention. However, the cause of late lesions is usually distinct.

Recovered bacterial microorganisms associated with cosmetic procedures usually include common skin and soft tissue pathogens, such as *Streptococcus aureus*. Patients usually present with single or multiple erythematous and/or fluctuant nodules, which can be treated with a short course of appropriate antibiotics. However, presentation of a new lesion more than 2 weeks postprocedure strongly suggests atypical infection, with mycobacteria being a possible culprit.[16,30] Patients usually present with a firm, mildly tender mass or nodule[16] with or without fluid. As a response to infection, patients may also experience systemic reactions, such as fever, leukocytosis, weight loss, and fatigue. In such cases, lesions should be aspirated or a biopsy should be performed, and the specimens should be sent for bacterial, fungal, and acid-fast stains and culture.[16] Up to four antimicrobial agents may be used if the lesion is identified as mycobacterial, depending on the severity of the infection and the possible duration of treatment. Disruption or removal of the injected lesion may also hasten recovery.[16]

Atypical or nontuberculous mycobacterial organisms are commonly found in the soil and water. In normal healthy individuals, the organisms tend to be associated with low pathogenicity, the exceptions being *Mycobacterium chelonae* and *Mycobacterium fortuitum*, which represent more serious strains. Although still uncommon, mycobacterial wound infections are being reported with greater frequency after cosmetic surgery.[16,30] Such outbreaks have been linked to surgery following inadequate chemical sterilization procedures or the use of quaternary ammonium compounds for sterilization.[31] However, a recent report has linked an outbreak of *Mycobacterium abscessus* infection after soft tissue augmentation with a hyaluronic acid derivative.[30,32] It is not known whether the material was contaminated with *M. abscessus* during manufacture or if the bacteria were inoculated during injection because administration occurred in a nonmedical setting.

Poor Technique and Adverse Reactions

Underscoring the need for product-specific training, the uneven distribution of injected products, because of poor technique, can also lead to lumps and nodules postinjection.[20,22] This is of particular concern with more permanent products because the undesired results are also long lasting. In the case of PMMA implants, for example, overaggressive injection may lead to irregularity or lumpiness, whereas if the product is placed too superficially, beading can occur.[12,14]

The correct placement of products minimizes the risk of adverse events. For example, local necrosis caused by vascular interruption at the site of injection has been noted with bovine collagen implants and hyaluronic acid–based products.[2,3,10,33–35] Since more than half of these events occurred in the glabellar area, physicians are cautioned against using anything other than the thinner fillers (eg, Zyderm I, CosmoDerm, Fine Hylaform, and Restylane Touch) at this site.[3,34] Poor injection technique has even led to partial vision loss after collagen therapy and is attributed to occlusion of the retinal artery.[5,36] Table 3 suggests the desired depth and sites of injection and the degree of correction required for various injectable products; undercorrection can mean transient or ineffective treatment, whereas too much correction can result in discoloration or irregularities. As a result of the frequency of adverse reactions, injection of some products, such as PMMA and Rooliesse (Bioform Medical, San Mateo, CA, USA), is not recommended for the lips.

Summary

By introducing a foreign substance into the dermis of subcutaneous compartments, some patients will exhibit hypersensitivy reactions; a foreign body reaction can be expected at the histologic level and, more rarely, at the clinical level. The incidence of clinically relevant foreign body reactions depends on the characteristics of the injected product.

To equip patients and physicians with the information they require to make informed treatment decisions, it is important that soft tissue reactions are not merely noted but evaluated in terms of their clinical and esthetic significance.[37] It is also desirable to distinguish reactions that occurred because a product is unsafe from reactions that occurred because the procedure was carried out improperly. To minimize the former, rigorous testing of new prod-

Table 3. Technical Considerations of Various Products

Product Name	*Location of Injection*	*Potentially Safe Sites for Injection*	*Degree of Correction*
New-Fill/Sculptra (Dermik, Berwyn, PA, USA)	Deep dermal–subcutaneous junction	Nasolabial folds, facial lipoatrophy (sunken cheeks), atrophic scars	Undercorrection Repeated treatments required 3–6 sessions
Restylane (Medicis Aesthetics Holdings Inc., Scotsdale, AZ, USA)	Mid-dermis	Nasolabial folds, lips, glabellar folds, vermilion of lips, periorbital	Correction but not overcorrection
Restylane Touch, Fine Hylaform (Medicis)	Upper dermis	Nasolabial folds, lips, glabellar folds, vermilion of lips, periorbital	Correction but not overcorrection
Restylane/Perlane, Hylaform Plus (Medicis)	Deep dermis	Nasolabial folds, lips, scars	Correction but not overcorrection
Restylane SubQ (Medicis)	Subcutaneous, over periosteum	Malar and chin. Other sites pending trials.	Correction
CosmoPlast and Zyplast (INAMED Aesthetics, Santa Barbara, CA, USA)	Mid-to-deep dermis	Lips, scars, nasolabial folds	Overcorrection by 125–150%
CosmoDerm and Zyderm I and II (INAMED Aesthetics)	Upper dermis	Lips vermilion border, glabellar folds	Overcorrection by 150%
Radiance (also Radiesse) (BioForm Medical, San Mateo, CA, USA)	Deep dermal–subcutaneous junction	Nasolabial folds, scars, caution with lips	Correction
Silicone	Deep dermis	Nasolabial folds, lips. Risk of nodules	Gradual correction but no overcorrection
Artecoll/Artefill (Artes Medical Inc, San Diego, CA ,USA)	Deep dermis	Nasolabial folds, scars; caution with lips. High risk of granulomas	Correction

ucts should be required, including long-term follow-up.[38] To minimize the latter, procedures should take place in a medical setting, ideally by trained dermasurgeons. Unfortunately, the medical literature surrounding cosmetic augmentation is inconsistent in its use of terminology: the reader may be provided with the incidence of an adverse event but with inadequate description of how such adverse events were classified. A case in point is the use of the word *granuloma*, which may mean anything from the presence of a giant cell to a reactive nodule with caseation. This lack of clarity hinders safety comparisons between products and renders informed decisions regarding treatment choice problematic.

When selecting a treatment, patients should be made aware of the results and the risks involved with undergoing procedures. Patients should be made aware that adverse reactions are more likely and more persistent with some products, and at certain injection sites, than others. Further collection and analysis of safety data associated with injectable agents are of great importance for potential patients.[38,39]

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