Recommendations and Treatment Options for Nodules and Other Filler Complications

Rhoda S. Narins, MD,* William P. Coleman, III, MD,† and Richard G. Glogau, MD‡

The authors have indicated no significant interest with commercial supporters in regards to this article.

All injectable fillers have side effects. The longer lasting a filler is in vivo, the more persistent the side effects can be and, thus, the more difficult to treat. That is why it is advisable to gain experience with a reversible filler before attempting to use those with more longevity. Many side effects are due to problems with injection technique and training and experience are needed to minimize these iatrogenic problems, but some problems may be due to inherent properties of the filler or unappreciated host factors.[1]

Patients taking anticoagulants may bruise more. Anecdotally, patients with chronic sinusitis, chronic dental problems, or other infections may have a greater tendency to develop an infection after a filler is injected in the periorbital area or central face. These patients also may be prone to formation of a biofilm around or in the implant caused by injection trauma around the site of a previous filler injection. Many problems that were previously assumed to be foreign body granulomas or allergic reactions on the basis of negative bacterial cultures are now thought to be due to biofilms.[2] Many biofilms are almost impossible to culture using current standard microbiology culture technology and therefore may initially be treated incorrectly with injections of intralesional steroids alone, instead of using two or three antibiotics.[3] As we gain more experience with different fillers, we learn more about the reactions that can develop with each, how to recognize them early, and how to treat them.[4]

Biofilms

It is important to understand how a biofilm can be responsible for many filler side effects, particularly those that present as late-onset angry red lumps and bumps. A biofilm is a complex aggregation of microorganisms marked by the excretion of an extracellular protective and adhesive matrix. This allows the development of a community of microorganisms characterized by surface attachment of a free-floating cell with subsequent genetic diversity and DNA changes with structural heterogeneity. This framework of excreted polymeric substance allows complex community interactions with enlargement of the biofilm as more and more cells join. This may lead to the development of increasing antibiotic resistance, sometimes requiring up to a 1,000 times greater concentration of a given drug, which demonstrates a high degree of specificity and activity when used against bacteria in the non-biofilm state. In addition, the adhesive extracellular matrix traps leucocytes, making them ineffective through immobility. This aggregate of antibiotic-resistant cells can now have complex chemical communications with water channels to distribute nutrients and promote bacterial cooperation. In a biofilm, there are many

*Clinical Professor Dermatology New York University School of Medicine, White Plains, NY; †Departments of Dermatology and Plastic Surgery, Tulane Health Sciences Center, New Orleans, LA; ‡Department of Dermatology, University of California-San Francisco, San Francisco, CA

ISSN: 1076-0512 • Dermatol Surg 2009;35:1667–1671 • DOI: 10.1111/j.1524-4725.2009.01335.x

dormant or persister cells that remain resistant to antibiotics. Biofilm populations can shift from active to dormant depending on exogenous threats. When bacterial proteins turn off cell metabolism and the cell becomes dormant, it becomes antibiotic resistant, as well as difficult, if not impossible, to culture. This explains why we have for so long failed to recognize these lumps occurring after filler injections as infections. This low-grade smoldering infection is characterized by low host response, high antibiotic resistance, and a low possibility of a positive culture. In addition, operative specimens are also usually negative on culture. Biofilm detection in biopsies requires the use of fluorescent DNA stains or other chemical reactions (see more in-depth discussion in this issue).

Many researchers feel that biofilms coat all implants, including breast and cheek implants, prosthetic joints, and heart valves. Manipulation, trauma, or the injection of another substance in close proximity can activate biofilms. This can result in a clinical picture of local infection, including an abscess or cellulitis, a systemic infection with sepsis, a granulomatous response with a foreign body granuloma or a nodule, or an inflammatory response. Biofilms may account for many of today's filler complications, including granulomas, nodules, inflammation, abscesses, and delayed reactions.

Particles

Although some fillers are dispersions of fibrils, some are homogenous gels, and some are particulate or particles in suspension, some are clearly more particulate than others. There are several things to consider when thinking about particles, including the size; the shape; the surface topology; whether it is smooth, spiky, rough, etc.; and the chemical composition of the particles. The chemical composition has many ramifications. Does the chemical induce collagen formation and to what degree? Is the particle hard or soft? Is it sticky, and will it clump? Can it be metabolized, or is it resistant to degradation and therefore potentially permanent? Does it occur naturally in human tissues like hyaluronic acids (HAs) and collagen, or not?

Some of these attributes may lead to negative or positive sequelae and some to both. The size of the particles is important because particles smaller than 20 μ in size can induce phagocytosis. Particles must be bigger to avoid foreign body reaction and provide durability. Larger particles have less of a tendency to migrate. The shape is important because sharp edges may irritate the tissues and cause foreign body reactions. The surface matters because sticky particles can clump and lead to lumps and bumps or help give the desired lift. The chemical composition is important because some chemicals can induce irritation or produce a great deal of unwanted fibroplasia, leading to lumps and bumps and more erythema and swelling. Anticoagulant properties of fillers can lead to more bruising. If the product absorbs water, there may be more swelling. HAs may have anticoagulant properties that lead to more bruising, they can absorb water that can lead to swelling, and they are flexible, which leads to less tissue reactivity. Juvederm (Allergan, Irvine, CA) (Food and Drug Administration (FDA) approved for nasolabial folds) is more cohesive (gives lift) softer, whereas Restylane (Medicis, Scottsdale, AZ) (FDA approved for nasolabial folds) is firmer (gives lift) and less cohesive, and Beletero (Merz, Greensboro, NC) (a non-FDA approved HA, available outside the United States), with cohesive polydensified matrix (CPM) technology, has varying densities and is claimed to fill between small spaces in the tissue (gives lift). The different characteristics of hardness, cohesiveness, and filling in tissue spaces all contribute to give a volumizing "lift." None of them are antigravitational. Each filler has its own set of properties, and noticeable differences in these attributes exist even between fillers in the same class or family of agents.

The size of the particles is always in a range, but some examples of sizes include Radiesse (Bioform, San Mateo, CA), 25 to 45 μ; Artefill, 30 to 50 μ; Restylane, 250 μ; Perlane (Medicis), 1,000 μ;

Juvederm, 50 to 500 μ (very cohesive); Sculptra (Sanofi-Aventis, East Rutherford, NJ), 40 to 60 μ up to 112 μ; and Dermalive (Dermatech, Paris, France), 45 to 65 μ average (range 20–120).

The size and firmness of the particles also matter. A larger needle may be needed for large and firm particles to eliminate clogging needles. Physical phenomena affect the flow characteristics of multiple particles into and through a tube. Because multiple particles may hit the opening of the needle in the hub at the same time while leaving the syringe, the probability of needle jams increases as the particle size increases. Most particulate products flow better through 27 G needles. Some of these fillers can flow through a 30 G needle, but the rate of jams increases substantially.

Particles with irregular surfaces and sizes are thought to have a higher inflammatory response. Spiky, sharp-edged particles that tend to clump after injection may cause problems with Dermalive. This filler has been removed from the market in Europe because of many reported reactions. Arteplast had many surface irregularities and carried a static electrical charge that attracted nanoparticles. It also had particles smaller than 20 μ that could be phagocytized. The updated version, Artefill, is a smooth, spherical filler that has no charge and no particles smaller than 20 μ. These changes may have reduced the risk of reactivity and a 1,000-patient prospective study is well into its first year. The substance was unavailable for awhile because the manufacturer filed for bankruptcy, but now it has been bought by Suneva and is available again. A skin test is still required for this product.

Juvederm, Restylane, Beletero, and other HAs are softer and more distensible than other particles, so there is less inflammation. HAs are also reversible (dissolvable) with hyaluronidase, which may offer a significant margin of safety over more persistent fillers.

There are many things to think about with particle and nonparticle fillers. Although injected particles do not flow as well as nonparticle fillers, they stay where placed and produce excellent volume replacement. On the other hand, the characteristics of the particles can lead to nodules, bumps, and other reactions.

Nodules and Bumps

The implants that are most susceptible to producing a biofilm and complications are the long-lasting or permanent fillers, the volumizing fillers, fillers injected as a mass volume, the encapsulated fillers such as Bio-Alcamid (Polymekon, Milan, Italy) (non-FDA approved and available only outside the United States), and the fillers that cause the most trauma in the tissue.[5]

Nodules and bumps can occur immediately after injection; can be intermediate in onset, occurring 2 weeks to 1 year after injection; or can be delayed, sometimes for many years. They can be noninflammatory and nonpainful or inflammatory and painful. Incorrect injection technique often causes those that are noninflammatory and nonpainful. The filler may be injected at the wrong level, usually too superficially, or too much filler can be injected into one area. Sometimes lumps are seen with substances such as polylactic acid (Sculptra—FDA approved in the United States for facial atrophy due to human immunodeficiency disease and cosmetic use) due to incorrect dilution of material or because the material continues over time to initiate fibrosis unevenly.

Algorithms for Treatment of Nodules and Bumps

If a patient has a nonpainful lump after a filler injection, the physician can reassure them that it will probably disappear if it is a HA and advise them to wait 1 to 2 weeks and watch it. If the patient is anxious, the physician can recommend massage and see the patient regularly to manage expectations and reassure.

TABLE 1. Filler Bumps and Nodules

1. Nonpainful, noninflammatory nodules: watch or massage
   Too much product injected?
   Incorrect technique of injection?
2. Painful inflammatory nodules: treat immediately
   Immediate onset
   Intermediate onset: 2 weeks to 1 year
   Delayed onset: after 1 year

Immediate painful nodules are probably due to an infection, and late-onset nodules are also probably due to an infection from activation of a biofilm. If the bump is red and painful, it is best to see the patient immediately and start an antibiotic as soon as possible, continuing for 2 to 6 weeks (Table 1). Clarithromycin 500 mg or minocycline 100 mg twice a day for 6 weeks will cover most early infections. The length of antibiotic treatment depends on the degree of infection, the duration of the infection, and whether the filler is a reversible HA that can be "removed" with hyaluronidase injections or is a longer-lasting particulate filler. More severe infections may require intravenous antibiotics followed by a course of oral antibiotics. Treat any inflammatory nodule as an infection. If the filler is a HA, hyaluronidase injections will dissolve the substance. Incision and drainage is also recommended to expel as much of the substance as possible (Table 2). Sometimes if a small incision is made over the filler, it can be expressed through the tiny opening. In other cases, a local anesthetic, such as lidocaine with epinephrine, can be injected over the nodule, and an empty syringe with a 16 G needle can be employed to extract the filler, using back pressure on the plunger. The evacuated material collected by either means should be sent for culture with prior discussion with the laboratory about the possibility of using special techniques to identify presence of biofilms. Routine culture results with biofilms are often negative.

TABLE 2. Algorithms of Treatment for Painful Inflammatory Nodules Early Onset

1. Oral antibiotics first for 2 to 6 weeks. Treat infections immediately
2. Incision and drainage if fluctuant and culture (HA)
3. Inject hyaluronidase if caused by HA
4. Do not use intralesional steroids

TABLE 3. Algorithms of Treatment for Painful Inflammatory Nodules

Late-onset or particulate fillers (presumed activation of a biofilm). Treat the active infection and then the biofilm

1. Antibiotics first and fast—may need 2 or 3 drugs
2. Incisional biopsy and then culture (routine microbiologic cultures often negative)
3. Intralesional injections of steroid considered here. MUST BE TAKING AN ANTIBIOTIC BEFORE USING!
4. Irrigation with an antibiotic (intralesional) and suction (Israeli protocol for BioAlkimid)
5. Heat plastic materials such as poly(methyl methacrylate) with a laser to melt and drain (Daniel Cassuto, MD)
6. Excision or debridement of nodule usually necessary but not always possible

If the substance injected is a longer-lasting particulate filler, excision must be considered if antibiotics and steroids do not work. Intralesional steroid injections should be used only if the patient is already taking an antibiotic, because steroids can make the inflammation much worse by further activating the biofilm.[3] In the case of Artecoll or Artefill (Suneva, San Diego, CA), dilutions of up to 40 mg/mL of triamcinolone acetonide must sometimes be injected intralesionally to treat the lumps. The patient must be warned that fat atrophy can occur as a result and may need to be treated and disguised with subsequent injections of HA (Table 3).

Once the filler is removed, the biofilm and the painful nodule will usually resolve. Most fillers are not reversible like the HAs are and are impossible to eliminate without excision. Many fillers also have limited life spans and will gradually disappear. The fillers most susceptible to complications from biofilms are combination gels such as collagen–

poly(methyl methacrylate) (PMMA) suspensions, HA–PMMA suspensions (Dermalive and Dermadeep, Dermatech, PMMA-HA), Bioplastique (silicone in polyvinylpyrrolidone), Evolution (ProCytech SA, Bordeaux, France, polyacrylamide-co-DADMA), Bio-Alcamid (polyalkylmide), and Outline (ProCytech, procollagen). Radiesse and homogenous gels such as silicone and the polyacrylamides are less likely to produce bilofilms but may do so, especially if adulterated or a large volume is injected at once.[6]

Treatment algorithms for inflammatory nodules differ depending on their onset and whether they are HAs. If the nodules or bumps are early onset or are from HA, the treatment (Table 1) differs from nodules or bumps that are late onset or from particulate fillers (Table 2). Dr. Daniel Cassuto has developed a method for melting and removing plastic PMMA fillers using a laser (Table 3).

References

1. Leonhardt JM, Lawrence N, Narins RS. Angioedema acute hypersensitivity reaction to injectable hyaluronic acid. Dermatol Surg 2005;31:577–9.
2. Wiest LG, Stolz W, Schroeder JA. Electron microscopic documentation of late changes in a permanent filler and clinical management of granulomas in affected patients. Dermatol Surg. 2009;35(Suppl 2): 1688–99.
3. Christensen LH. Host tissue interaction, fate and risks of degradable and nondegradable gel fillers. Dermatol Surg 2009;35(Suppl 2): 1612–19.
4. Narins RS. Minimizing adverse events associated with Poly-L-lactic acid injection. Dermatol Surg 2008;34(Suppl 1):S100–4.
5. Narins RS, Jewell M, Rubin M, et al. Clinical conference: management of rare events following dermal fillers–focal necrosis and angry red bumps. Dermatol Surg 2006;32:426–34.
6. Narins RS, Beer K. Injectable liquid silicone: a review of its history, immunology, technical considerations, complications and potential. Plast Reconstr Surg 2006;118(3 Suppl):778–848.

Address correspondence and reprint requests to: Rhoda S. Narins, MD, Director Dermatology Surgery and Laser Center, 222 Westchester Avenue, White Plains, NY 10604