Calcium Hydroxylapatite Filler Foreign Body Granulomas: A Case Report of a Rare Occurrence and Review of the Literature

Laurel R. Schwartz, MD; Christina Thompson, BBA; Carmen Campanelli, MD

Calcium hydroxylapatite (CaHA) is approved by the US Food and Drug Administration for the correction of wrinkles and folds such as the nasolabial folds and human immunodeficiency virus–associated lipodystrophy. We report a rare case of foreign body granuloma formation in a 47-year-old woman who developed a persistent nodule on the left side of the upper lip following injection with CaHA in the lower face. We also discuss potential etiologies for this unpredictable reaction.

With a growing arsenal of filler materials available for cosmetic use, soft tissue augmentation with dermal fillers is a popular nonsurgical treatment option for facial rhytides. A popular combination gel and particulate is composed of calcium hydroxylapatite (CaHA), a natural component of bone and teeth. With an extensive safety profile based on its use in other medical capacities, CaHA has a low incidence of adverse reactions that generally are injection related and resolve within 2 weeks of the procedure.[1] Reasons for the formation of foreign body granulomas are not entirely understood, though certain characteristics make some filler materials more prone to this complication than others.

Dr. Schwartz is from the Philadelphia Institute of Dermatology, Fort Washington, Pennsylvania. Ms. Thompson was from Yardley Dermatology Associates, Pennsylvania, and currently is from NeoStrata Company, Inc, Princeton, New Jersey. Dr. Campanelli is from the Department of Dermatology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania; the Department of Dermatology, University of Pennsylvania, Philadelphia; and Yardley Dermatology Associates.

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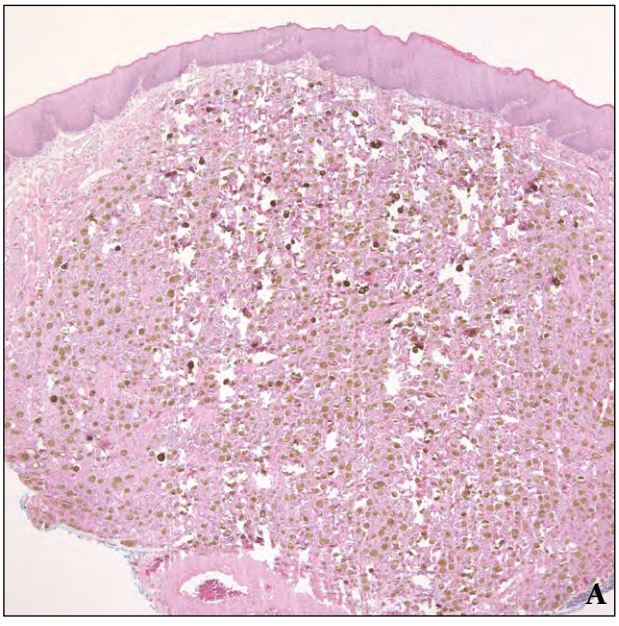
Correspondence: Christina Thompson, BBA, 15 Woodmere Way, Pennington, NJ 08534 (christina1516@comcast.net).

CASE REPORT

A 47-year-old woman presented to her dermatologist for soft tissue augmentation of the nasolabial folds. Calcium hydroxylapatite injections were administered with excellent results, which led the patient to seek additional CaHA injections in the nasolabial folds and marionette lines 5 months later. Approximately 6 months after the additional injections, the patient began to experience a sensation similar to the prodromal phase of a herpes simplex outbreak on the left side of the upper lip and noted a hard bump along the labial mucosa surface over the left canine tooth. The bruiselike nodule progressed in size despite treatment with topical, oral, and intralesional steroids. Three months later, the submucosal lump was excised via an intraoral approach.

Histopathology of the lump revealed an unencapsulated pandermal and intramuscular collection of evenly spaced, spherical foreign bodies, some with concentric laminations, each surrounded by multinucleated giant cells with numerous histiocytes, fibrocytes, and collagen fibers in the intervening stroma (Figure 1). Although the majority of the microspheres were intact, degenerative changes in several microsphere particles were noted. A von Kossa stain revealed minute flecks of calcium within individual microspheres (Figure 2).

Following excision, the nodule returned 2 months later and was reexcised using a similar approach. The reexcision specimen revealed a similar histology with multiple foreign body, multinucleated giant cells surrounding individual microspheres of CaHA. Following reexcision, the nodule returned and has subsequently been treated with weekly to bimonthly intralesional steroid injections, remaining localized to the same area.



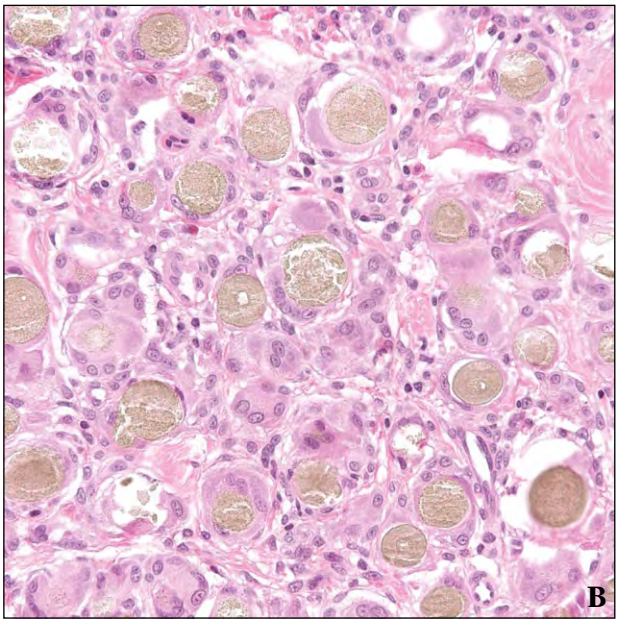


Figure 1. At scanning magnification, there is an unencapsulated pandermal infiltrate of calcium hydroxylapatite microspheres accompanied by a multinucleated giant cell reaction (A)(H&E, original magnification ×4). High-power magnification reveals largely intact individual microspheres surrounded by multinucleated giant cells with a sparse intervening fibrohistiocytic and collagenous stroma (B)(H&E, original magnification ×40).

COMMENT

Calcium hydroxylapatite is composed of uniform, 25- to 45-μm diameter particulate microspheres (30%) suspended in a carboxymethylcellulose, glycerin, and sterile water gel carrier (70%).[1,2] It naturally occurs in the human body as the inorganic constituent of bone and teeth[1]; therefore, CaHA filler is highly biocompatible, nontoxic, nonirritating, and nonantigenic, with an extensive safety profile and minimal inflammatory response.[1,3] With no known allergenic properties, CaHA does not require a pretreatment skin test and can be stored at room temperature.[4] Approved by the US Food and Drug Administration in 2006 for the correction of wrinkles and folds such as the nasolabial folds and human immunodeficiency virus–associated lipodystrophy, CaHA has been used for more than 20 years in various medical capacities,

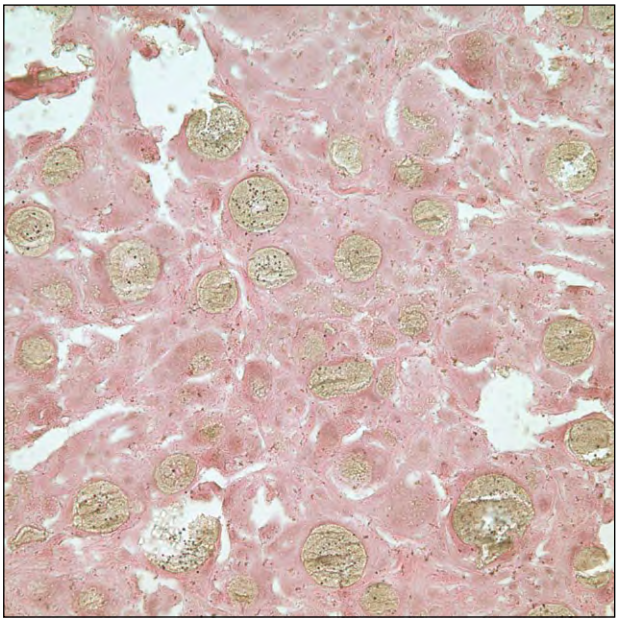


Figure 2. Minute specks of calcium were found within individual microspheres (von Kossa, original magnification ×40).

such as vocal cord paralysis, oral surgery, and radiology.[3,5] Common adverse reactions to CaHA filler include redness, swelling, bruising, and occasional lumpiness immediately following injection. There are no known reports of migration of the filler material or dystrophic osteogenesis when used for soft tissue augmentation.[3,4] The small pore size of CaHA particles appears to discourage fibrovascular and bony ingrowth in the soft tissue, as opposed to the macroporous CaHA used to correct maxillofacial defects.[6]

Despite some claims that it is the closest product to the ideal filler, foreign body granuloma formation still is a potential complication of CaHA injection.[4] The incidence rate of true foreign body granulomatous reactions to CaHA is unknown, and published reports are rare. To our knowledge, the sole case of a foreign body granulomatous reaction to CaHA was reported by Sankar and McGuff[7] in 2007 when a 51-year-old woman presented to an oral medicine clinic with a lump on the mucosal lower lip. The patient previously underwent CaHA injections, but the timing of the formation of the lump relative to the procedure was unknown. Histologic examination revealed a sclerosing granulomatous response with multinucleated giant cells surrounding individual microspheres of CaHA, interspersed fibrosis, and chronic inflammation[7]; these findings are similar to our case.

In a 2009 report, Lemperle et al[5] described 2 cases of true granuloma formation in 35,000 men who received treatment with CaHA for correction of depressed acne scars in the cheeks. The authors observed that the reaction extended beyond the site of injection. Although the largest inflamed areas were excised, no histologic findings were reported.[5] The histology reports provided by Jansen and Graivier[8] to support the diagnosis of lip nodule complications in a study of 609 patients who received CaHA injections for facial soft tissue augmentation are more consistent with foreign body granulomas. The formation of lip nodules (lumps that developed within 6–12 weeks of injection) was reported in 42 of 338 (12.4%) patients who had received lip mucosa injections and 6 of 163 (3.7%) patients who had treatment for radial lip lines. Most nodules resolved following intralesional steroid injections or massage; in nonresponders, lesions were excised. The authors did not indicate how many patients required excision and did not distinguish between those with granulomatous giant cell reactions and those with densely packed CaHA deposits within a fibrotic stroma.[8] Although no chronic granulomatous formations were apparent, nodule formation was consistent with true foreign body granulomas (sclerosing granuloma), with a histologic presentation similar to our patient.

Despite its high biocompatibility profile, the formation of true foreign body granulomas in patients injected with CaHA illustrates that any facial filler can produce a granulomatous response. The volume of filler that is injected is thought to be one cause, though it is not universally apparent in every case of granuloma formation.[5] Some investigators have noted a decrease in lip nodule formation when filler volume was reduced, when technique was improved, and when the clinician's experience and comfort level with the product increased.[4,8] In his review of facial fillers, Bentkover[9] noted that particle size is important in the phagocytic response because particles that are 15 to 20 μm can be phagocytosed by macrophages, as demonstrated by fillers containing polymethyl methacrylate microspheres in which a decrease in granuloma formation was concurrently noted with a decrease in the number of small particles (<20 μm).[5,10] The particle size of CaHA microspheres is larger than the threshold size for phagocytosis, which suggests an additional reason CaHA is thought to have a low incidence of foreign body granuloma formation. Surfaces that are irregularly shaped with angles (eg, nasolabial folds) also are more likely to promote granuloma formation than smooth surfaces of microspheres.[2,5,10] Hydrophobicity, cross-linking, concentration, surface charge, and immunogenicity also play a role in the body's response to foreign injected materials.[9]

Severe systemic infections, trauma, drugs, and diseases reportedly have been associated with several cases of foreign body granulomas.[5] Negative results have been reported with cultures, Gram stain, or polymerase chain reaction of granulomatous responses of adverse reactions to injected material in patients treated with combination gel fillers, such as microparticles dissolved in a degradable polymer gel including CaHA. Christensen[11] reported adverse reactions to polyacrylamide gel, a permanent hydrophilic homogeneous polymer gel (hydrogel), in which 55 of 40,000 patients showed an infectious etiology with bacteria of low virulence. Symptoms cleared with early treatment with antibiotics but were refractory in cases of delayed treatment, steroid use, or large doses of nonsteroidal anti-inflammatory drugs administered instead of or concurrently with antibiotics.[11] A similar study by Burmølle et al[12] involving the same filler material identified bacteria in biopsies of 3 of 8 (38%) patients with adverse reactions after injection using hematoxylin and eosin as well as Gram stain. The sensitivity of bacterial detection, mostly of cocci, increased to 7 of 8 (88%) cases with fluorescence in situ hybridization with peptide nucleic acid probes targeting all bacterial species.[12] This low-grade bacterial infection, thought to be induced during injection, is postulated to mount little host response and has high antibiotic resistance. Studies of permanent filler gels such as these suggest that bacteria may still be responsible for idiosyncratic foreign body granulomatous

responses in cases of combination particulate gels.[10,11] In addition to granulomas, further complications such as nodules, abscesses, inflammation, and delayed reactions can occur from biofilm bacterial colonies. Thus, the early treatment of all inflammatory nodules, regardless of timing of onset, is recommended with a course of oral antibiotics for several weeks.[10]

CONCLUSION

Although they are rare, cases of foreign body granulomatous responses to CaHA injections are a reminder that any facial filler can cause this adverse reaction, which presents a challenge for dermatologists, as the presence of histiocytes and multinucleated giant cells may be characteristics of the normal incorporation of injected material or a response to a large collection of unequally distributed material (a nodule). Granuloma formations are caused by a combination of factors, including filler composition and characteristics, but the reasons for these reactions remain unknown. Additional research on the postulated formation of a protective bacterial biofilm community, which provides an inflammatory nidus for the immune system but protects the bacteria from conventional detection techniques, is needed.

REFERENCES

1. Jacovella PF. Use of calcium hydroxylapatite (Radiesse) for facial augmentation. *Clin Interv Aging.* 2008;3:161-174.
2. Lemperle G, Morhenn V, Charrier U. Human histology and persistence of various injectable filler substances for soft tissue augmentation [published online ahead of print December 4, 2003]. *Aesthetic Plast Surg.* 2003;27:354-366; discussion 367.
3. Graivier MH, Bass LS, Busso M, et al. Calcium hydroxylapatite (Radiesse) for correction of the mid- and lower face: consensus recommendations. *Plast Reconstr Surg.* 2007;120(suppl 6):55S-66S.
4. Roy D, Sadick N, Mangat D. Clinical trial of a novel filler material for soft tissue augmentation of the face containing synthetic calcium hydroxylapatite microspheres. *Dermatol Surg.* 2006;32:1134-1139.
5. Lemperle G, Gauthier-Hazan N, Wolters M, et al. Foreign body granulomas after all injectable dermal fillers: part 1. possible causes. *Plast Reconstr Surg.* 2009;123:1842-1863.
6. Berlin AL, Hussain M, Goldberg DJ. Calcium hydroxylapatite filler for facial rejuvenation: a histologic and immunohistochemical analysis. *Dermatol Surg.* 2008;34(suppl 1):S64-S67.
7. Sankar V, McGuff HS. Foreign body reaction to calcium hydroxylapatite after lip augmentation. *J Am Dent Assoc.* 2007;138:1093-1096.
8. Jansen DA, Graivier MH. Evaluation of a calcium hydroxylapatite-based implant (Radiesse) for facial soft-tissue augmentation. *Plast Reconstr Surg.* 2006;118(suppl 3):22S-30S; discussion 31S-33S.
9. Bentkover SH. The biology of facial fillers [published online ahead of print May 4, 2009]. *Facial Plast Surg.* 2009;25:73-85.
10. Narins RS, Coleman WP 3rd, Glogau RG. Recommendations and treatment options for nodules and other filler complications. *Dermatol Surg.* 2009;35(suppl 2):1667-1671.
11. Christensen LH. Host tissue interaction, fate, and risks of degradable and nondegradable gel fillers. *Dermatol Surg.* 2009;35(suppl 2):1612-1619.
12. Burmølle M, Thomsen TR, Fazli M, et al. Biofilms in chronic infections—a matter of opportunity—monospecies biofilms in multispecies infections [published online ahead of print June 7, 2010]. *FEMS Immun Med Microbiol.* 2010;59:324-336.