OBSERVATION

Cosmetic Permanent Fillers for Soft Tissue Augmentation

A New Contraindication for Interferon Therapies

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Background: Most of the new fillers used for soft tissue augmentation in aesthetic dermatology are considered well tolerated, but very little data are available on their long-term tolerability, especially in patients receiving immunomodulatory therapy.

Observations: A 48-year-old woman presented with disfiguring facial edema 10 weeks after she began antiviral therapy with peginterferon alfa-2a and ribavirin for chronic hepatitis C infection. The major affected sites had been treated 10 years before with Artecoll, a permanent filler containing polymethylmethacrylate. A treatment attempt with allopurinol was initiated while antiviral therapy was continued and was successfully completed after 6 months. Despite significant improvement, extended plastic surgery was necessary for facial reconstruction.

Conclusions: The normal host response to a cosmetic filler is a weak granulomatous reaction. Interferon and other immunostimulatory medications can lead to an exacerbation of this preexisting low-grade chronic inflammation that is quite similar to interferon-triggered sarcoidosis. This potential long-term risk has medicolegal implications for informed consent and for the potential use of both permanent fillers and interferon.

Arch Dermatol. 2007;143:507-510

SOFT TISSUE AUGMENTATION IS a common procedure, for which a wide variety of cosmetic fillers are used. The target group for these interventions for cosmetic or rejuvenation purposes is mainly composed of middle-aged women. The main aims are to smooth wrinkles or creases in perioral, periocular, and cheek areas and to produce an artificial augmentation of lip or cheek volume. These procedures are sometimes performed in individuals who might need immunomodulatory therapy years later for a life-threatening disease such as chronic hepatitis C infection or malignant melanoma. Most of the new fillers are considered well tolerated. Injectable aesthetic microimplants such as Bioplastique, Artecoll, and Dermalive are highly regarded because they are inert like silicone, tend not to migrate in the tissue because of the induction of human collagen production, and usually do not induce much of a host immune response. A certain degree of low-grade inflammation due to the use of cosmetic fillers is unavoidable; this inflammation is the likely link for interactions between cosmetic fillers and interferon. To our knowledge, the interaction of cosmetic fillers and interferons has not been described in the medical literature or manufacturer databases, but we recently encountered such a problem.

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REPORT OF A CASE

A 48-year old woman received subcutaneous injections of peginterferon alfa-2a (80 µg/wk) and oral ribavirin therapy (400 mg/d) for chronic hepatitis C infection. Ten weeks after the initiation of therapy, she presented with a 2-week history of progressive disfiguring facial edema. She had blue-red swelling mainly involving the upper and lower lips, nasolabial grooves, and glabella (**Figure 1**). Ten year earlier, these sites had been treated with the polymethylmethacrylate (PMMA)-containing cosmetic permanent filler Artecoll (Artes Medical Inc, San Diego, Calif) to smooth wrinkles and to augment the lips. There was no history of sarcoidosis or tuberculosis. A subcutaneous papule was palpable in an appendectomy scar on physical examination, but no changes were detectable in the scars from breast augmentation surgery. An x-ray film of the

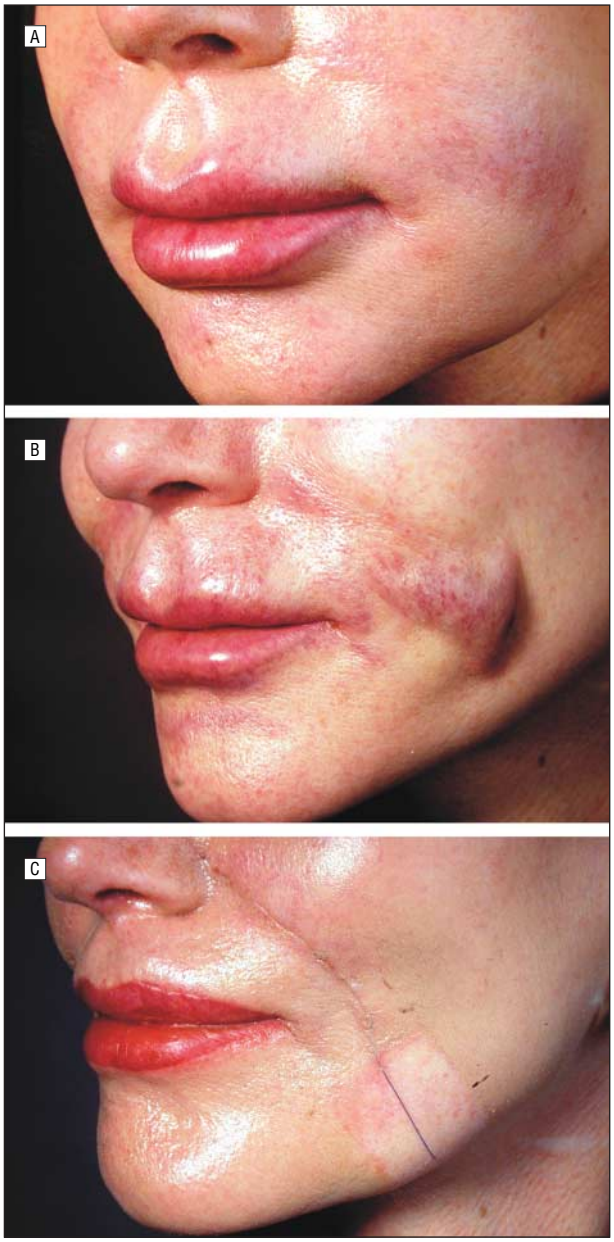

Figure 1. Swelling of the lips and formation of a cyst along the left nasolabial groove at presentation (A), after 15 weeks (B), and 9 days after the fifth plastic surgery (C).

chest showed no sign of hilar lymphadenopathy. The angiotensin-converting enzyme level was elevated at 43 U/L (reference range, 8-21 U/L). Antiviral therapy was continued at the same dosage. Oral allopurinol therapy was initiated at a maximum dose of 600 mg/d, because of a previous report describing its efficacy in the treatment of PMMA granulomas.[1] Six weeks later, the facial swelling was slowly decreasing, but no significant fading of the discoloration had occurred. Ten weeks after the patient's initial visit to our dermatology department, cystic nodules appeared along nasolabial grooves, and at 15 weeks there was an expanding ulcer in the glabellar region. Antiviral therapy was completed as scheduled after 6 months. No virus load was observed at the end of antiviral therapy or during follow-up. Noticeable improvement of facial edema accentuated the discoloration of the injected sites as well as the nodules along nasolabial grooves. Ultrasonographic examination of the nodule on the left side of the face demonstrated a septate cyst measuring $55 \times 11 \times 7.5$ mm in diameter with dorsal sonic enhancement. For diagnostic and therapeutic purposes, the lesion was excised. Histologic examination revealed a dense sarcoidal granulomatous infiltrate at the dermal-subcutaneous fat border surrounding densely packed, small, round cystic spaces that contained translucent, nonbirefringent, uniformly sized microspheres (**Figure 2**). On electron microscopy, some of the microspheres had lost their smooth surface, while others had leaked into the surrounding tissue. The subcutaneous papule in the appendectomy scar was excised at the same time and showed sarcoidal granulomatous dermal infiltrates with giant cells engulfing birefringent foreign material, most likely suture remnants. During the next 16 weeks of allopurinol therapy, the discoloration at the injection sites improved, the nodules along the nasolabial grooves partially resolved, and the glabellar ulcer healed spontaneously. Allopurinol therapy was discontinued after 8 months. Except for an insignificant increase in liver enzyme levels and a slight hair loss, the therapy was well tolerated. The decrease in uric acid levels showed that the patient had been compliant for the entire period. Despite this impressive improvement, 5 surgeries were required for facial reconstruction over the next 8 months. The last follow-up visit occurred 17 months after the first contact. An x-ray film of the chest still showed no sign of hilar lymphadenopathy. The angiotensin-converting enzyme level had decreased but was still slightly elevated at 30 U/L. There was no relapse of hepatitis C.

COMMENT

Artecoll is a injectable permanent cosmetic filler with a biphasic structure: fine 32- to 40-μm-diameter PMMA microspheres (solid phase) are suspended in a solution containing 3.5% bovine collagen solution and 0.3% lidocaine hydrochloride (liquid phase). The filler has to be placed at the dermal-subcutaneous fat border by means of a pretunneling injection technique. After the implant is placed, the collagen carrier is phagocytized by macrophages over 3 months and replaced by human fibroblasts and collagen fibers, which fix the PMMA microspheres. The permanent cosmetic fillers that are mainly being used at present (eg, Artecoll, Bioplastique, Dermalive, Dermadeep, Dow Corning, and Silskin) are generally considered to be well tolerated. Filler-induced granulomas are a rare adverse effect and cannot always be clearly distinguished from "nodules" that are caused by uneven tissue distribution of the product. Most filler-induced granulomas, such as asymptomatic dermal papules or nodules,[2,3] are excised because of unsatisfactory cosmetic results. Histologic examination of these cases showed that the type of granuloma depends on the type of cosmetic filler that is used.[1-4] Fillers that contain PMMA microspheres (eg, Artecoll) or acrylic hydrogel particles (eg, Dermalive) can cause foreign body–type granulo-

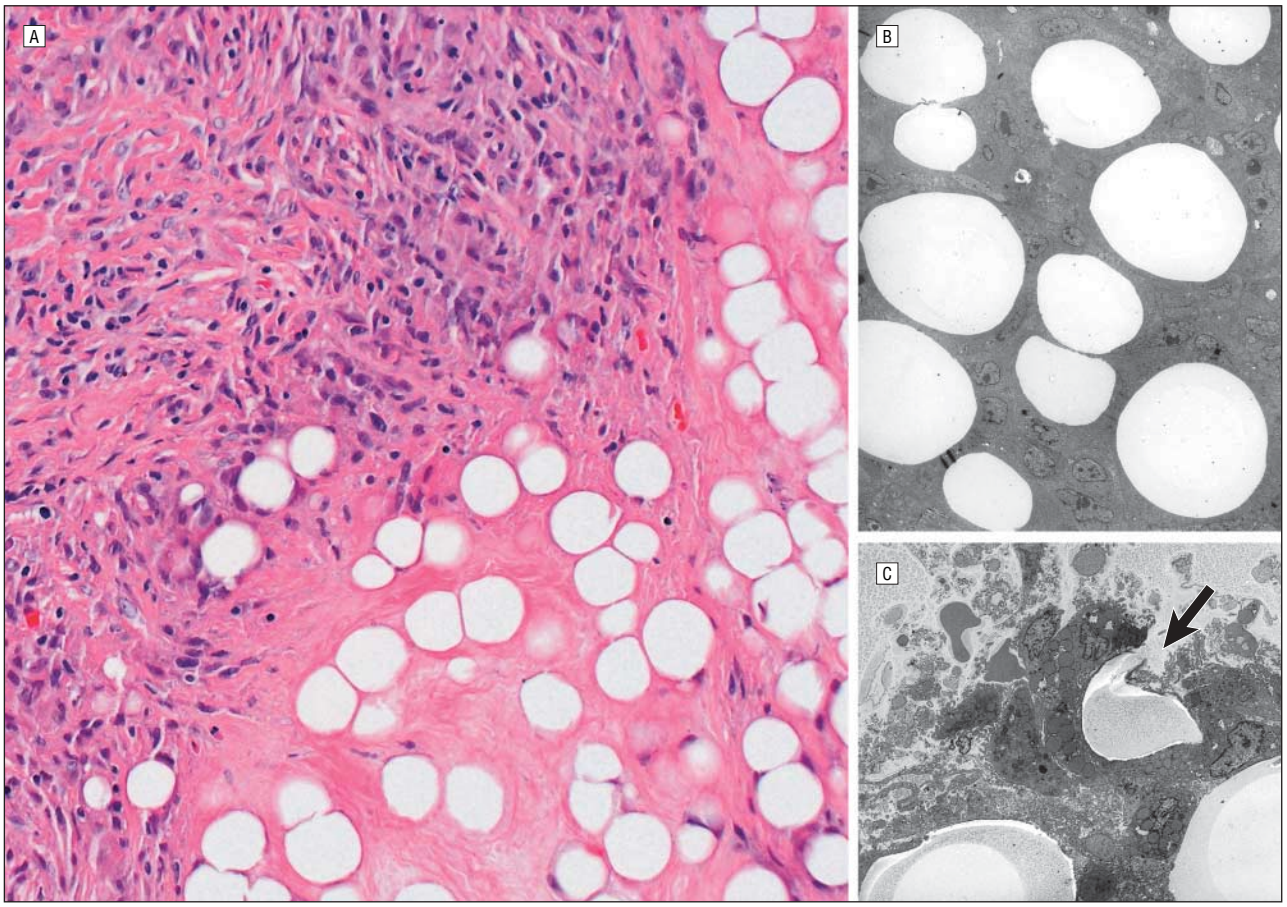

Figure 2. Histologic examination showed sarcoidal granulomatous infiltrates surrounding densely packed, small, round cystic spaces containing translucent nonbirefringent microspheres of approximately the same size (A); on electron microscopy, some of the microspheres showed a change in their smooth surface and leakage into surrounding tissue (B and C [arrow]).

mas that are consistent with sarcoidal granulomas.[1-4] Fillers containing silicone (eg, Bioplastique) can induce cystic and macrophagic-type granulomas.[3,4] More severe cases with blue-red discoloration or large areas of involvement are rare and tend to appear years after the injections.[1,2,4] The cases that have been reported have involved Artecoll and Dermalive.[1,2,4] To our knowledge, there have been no previous reports of persistent severe facial edema. Another unique aspect of the present case is the gravity-dependent formation of cystic lesions at the inferior aspects of the nasolabial grooves, which argues against the assumption that PMMA microspheres do not migrate because they induce anchoring human collagen. High-grade inflammation seems to mobilize the microspheres by inducing collagenases. This observation has its histologic correlate in the densely packed nonbirefringent microspheres without the expected intertwined collagen fibers. Polymethylmethacrylate is an inert material that is widely used in industry (Plexiglas), dentistry (Palavit), and medicine (Palacos) under difficult mechanic and chemical conditions. The electron microscopic findings of changes in the smooth surface of the microspheres and leakage in the surrounding tissue raise the question about how inert this material really is in the micromilieu of severe chronic inflammation.

The interferon-triggered inflammatory response of filler-associated granulomas is a new observation. Interferon-associated sarcoidosis is a rare but documented occurrence.[5,6] In larger series of patients with hepatitis C treated with interferon and ribavirin, new cases of sarcoidosis have occasionally appeared, with a prevalence of 0.2%.[5] Mainly middle-aged women have been affected during the first 6 months of antiviral therapy. Cutaneous and articular involvement were more frequent and hilar and extrapulmonary lymphadenopathy were less common in patients with interferon-triggered sarcoidosis than in those with non–interferon-triggered sarcoidosis. The prognosis of patients with interferon-triggered sarcoidosis is good. Improvement or spontaneous remission is clearly related to the discontinuation of antiviral therapy. Cutaneous manifestations may even resolve spontaneously during therapy. In one study, systemic steroids were required in 35% of individuals and had a negative effect on the outcome of antiviral therapy. The observations on interferon-triggered sarcoidosis closely match our case. Elevated angiotensin-converting enzyme levels and sarcoidal granulomas around both suture material and cosmetic filler also suggest cutaneous sarcoidosis in our case. Based on the observations regarding sarcoidosis in patients with cosmetic tattoos, the question as to whether the presence of polarizable foreign material within sarcoidal granulomas is compatible with the diagnosis of sarcoidosis is currently being debated in the literature.[7] The normal host

response to cosmetic fillers is a granulomatous reaction. In our opinion, interferon can cause an exacerbation of preexisting low-grade chronic inflammation that should not be equated with cutaneous sarcoidosis. Nonetheless, the immunological mechanisms of T_H1 response seem to be the same as in interferon-triggered sarcoidosis.

In our case, treatment with allopurinol at a maximum dose of 600 mg/d was well tolerated and did not interfere with the outcome of antiviral therapy. Allopurinol is thought to modulate inflammation as a free radical scavenger. It appears to produce a definite but slow and partial improvement, although completely separating its benefits from spontaneous improvement, especially after antiviral therapy is discontinued, is not possible.

This report demonstrates the potential long-term risks and touches on the medicolegal implications of cosmetic intervention with injectable aesthetic microimplants. The risk of severe interaction with interferon or other immunostimulatory medications should be included in the consent form for injectable aesthetic microimplants. Because patients often fail to mention cosmetic procedures, physicians should ask about a possible history of permanent soft tissue augmentation before prescribing interferon, and then in cases in which a permanent filler is present, they should review the indications for interferon and other immunostimulatory medications very carefully.

Accepted for Publication: October 31, 2006.
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Financial Disclosure: None reported.
Acknowledgment: We thank Hannelore Bischof, Birgit Fehrenbacher, Helga Möller, and Renate Nordin, University of Tübingen, Germany, for excellent technical assistance and Walter Burgdorf, MD, University of Munich, Munich, Germany, for critical review of the manuscript.

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