

SECTION EDITOR: GEORGE J. HRUZA, MD; ASSISTANT SECTION EDITORS: DEE ANNA GLASER, MD; ELAINE SIEGFRIED, MD

Foreign Body Granulomas Caused by Polymethylmethacrylate Microspheres



Successful Treatment With Allopurinol

Eva-Maria Reisberger, MD; Michael Landthaler, MD; Luitgard Wiest, MD; Josef Schröder, MD; Wilhelm Stolz, MD; Departments of Dermatology (Drs Reisberger, Landthaler, and Stolz) and Pathology (Dr Schröder), University of Regensburg, Regensburg, Germany. Dr Wiest is in private practice in Munich, Germany

The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 61-year-old woman was referred to our clinic with livid, red, firm nodules, tender to pressure, along the horizontal and vertical wrinkles of her forehead (**Figure 1A**). The patient reported significant swelling and redness of her entire forehead and eyelids that had occurred “overnight” about 6 weeks previously and disappeared spontaneously within 2 days. After regression of the swelling, persistent confluent nodules became apparent. The patient had discontinued a yearlong regimen of β -blockers without effect because her family physician suspected a drug-induced angioedema. A thorough examination of the patient’s history revealed injections of a polymethylmethacrylate (PMMA) and collagen mixture (hereinafter, Artecoll; Rofil Medical International, Breda, the Netherlands) into the forehead area 6 years prior for the correction of wrinkles, initially with 0.5 mL followed by 2.0 mL 4 weeks later. During the first 5 years after injection, the patient showed no symptoms (eg, hardening and pain) and no infections or autoimmune diseases.

A biopsy was performed for histopathologic and electron microscopic examination. Since the differential diagnosis included sarcoid granulomas, radiography of the chest, ultrasound examination of the lymph nodes, and measurement of the angiotensin-converting enzyme level in the serum were performed without any abnormal findings. In addition, the results of patch tests with acrylates were negative, excluding delayed-type allergy to PMMA, which is a component of Artecoll in the form of microspheres.

THERAPEUTIC CHALLENGE

Our goal was to effectively and noninvasively reduce the foreign body granulomas while minimizing the risk of destruction of the aesthetic result achieved by the implantation of the PMMA microspheres. The large extent of granulomas involving the entire forehead precluded surgical removal. Topical treatment was not considered because of the depth and severity of the lesions.

SOLUTION

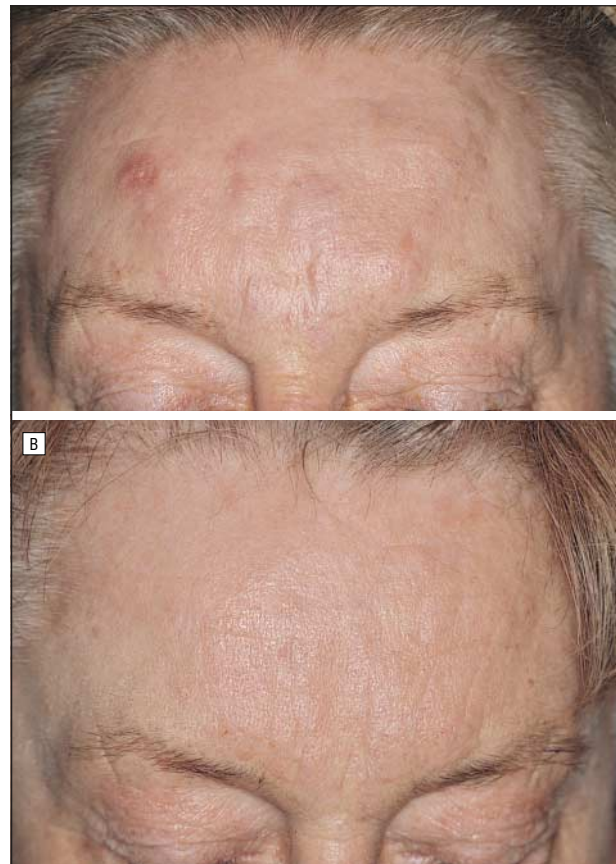


Figure 1. Livid, red nodules along the wrinkles of patient’s forehead before treatment with allopurinol (A) and after 22 weeks of therapy (B).

Treatment with allopurinol was initiated at 200 mg/d and increased to a maximum of 600 mg/d after 4 weeks. It was well tolerated, and after 8 weeks the patient reported less tenderness to pressure and a slightly decreased erythema. Over the next 8 weeks, the area became softer and less purple. Small, residual nodules along the glabella furrows that remained were treated with a

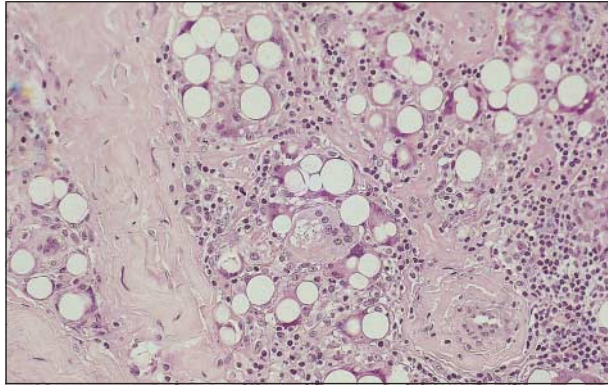


Figure 2. Granulomatous infiltrate with numerous multinucleate giant cells, histiocytes, and lymphocytes surrounding apparently empty cystic structures (hematoxylin-eosin; original magnification $\times 100$).

fludrocortide ointment (Sermaka; Lilly, Bad Homburg, Germany). Six weeks later, only slight discoloration was found on physical examination (Figure 1B). No dysesthesia was reported, and the former nodules were only palpable. Treatment was discontinued after a total of 24 weeks, and a follow-up examination 5 months later showed persistence of the good clinical result.

COMMENT

Nowadays, several alloplastic or autologous materials are available for the treatment of wrinkles and other soft tissue defects. Bovine collagen solution as well as autologous fat, hyaluronic acid preparations, liquid silicone, gold and expanded polytetrafluoroethylene threads, poly-L-lactic acid, and PMMA are widely used. Artecoll contains PMMA, providing the advantage of longer-lasting results than biological substances. It is composed of fine PMMA microspheres 30 to 40 μm in diameter with smooth surfaces suspended 1:3 in a 3.5% bovine collagen solution with the addition of lidocaine and should be implanted strictly into the deep layers of the dermis with a 27-gauge needle. Collagen solution is used as a carrier and represents 75% of the Artecoll implant. According to the literature, collagen is phagocytized by macrophages within 1 to 3 months after implantation and replaced by human fibroblasts and collagen fibers. It is calculated that approximately 50% of the implanted volume will be replaced (ie, at least two thirds of the entire Artecoll implant remains). This combination leads to the persistent aesthetic result.¹⁻⁴

Specimens from human volunteers were histologically examined at certain intervals to prove the biocompatibility of PMMA microspheres and to investigate the "normal" host response.² After 3 days, monocytes had thoroughly invaded the implant. Within the following 6 days, monocytes differentiated to fibroblasts. Nine days after the implantation, the microspheres were totally covered by tissue, and a fibrous capsule developed around the entire implant. After 2 to 3 weeks, connective tissue strands formed compartments dividing the microspheres into clusters, and vascularization became apparent. At this time, the first autologous collagen fibers could be detected, and their density increased until the fourth month when vascularization and active fibrosing seemed

to end. Foreign body giant cells were reported after the first week, reaching their maximum number after 3 weeks (a comparably small number of up to 1.5% of all cells), and this number remained constant after 2 months. Although a proper histologic long-term evaluation of PMMA microspheres subcutaneously injected into humans has not been reported, it is postulated that there is no change in this histologic picture after about 6 months.

However, the late development of massive giant cell formation around an implant indicates foreign body granuloma.⁵ This has been defined as multinucleated giant cells surrounded by palisading macrophages enveloped in a halo of lymphocytes. In contrast to this, a monolayer of macrophages surrounded by a zone of fibrous tissue is found at the surface of an implant as a sign of optimal biocompatibility. The well-tolerated filler should be enveloped with fibrocytes that remain in steady state with the implant for the rest of the recipient's life.⁵

In general, all synthetic polymer implants lead to some inflammatory response either by surgical trauma or by interactions of the tissue with the implant.^{6,7} When the polymer is exposed to the biological environment, its surface is first coated with a layer of proteins,⁶ preferably adsorbed proteins. The extent of possibly uncoated surface structures of the polymer depend on its physicochemical properties and its surface characteristics. The intensity of macrophage activity is influenced by these proteins and the quality of uncoated surface structures. Attraction of numerous macrophages and phagocytosis has so far been mainly described for particles with a rough or porous surface and a small size of up to 15 μm .⁷⁻⁹ Chronic inflammation frequently resulting in undesirable capsule fibrosis may follow the phagocytosis of synthetic implants with irregular surface characteristics. On the other hand, it is assumed that PMMA microspheres cannot be phagocytized or removed, and the material is believed to be permanently deposited because of its larger size and completely smooth surface.^{1,2} Thus, the risk of developing granulomatous foreign body reactions after correct subdermal implantation is widely denied, even though no experimental or clinical studies exist that would support this assumption.

In recent years, several reports have described adverse effects such as painful and disfiguring granulomatous skin lesions weeks or even years after implantation of PMMA microspheres.¹⁰⁻¹² According to these case reports, unsatisfactory cosmetic effects or visible, painful nodules led to excision of the material. Subsequent histopathologic and ultrastructural examination showed the distinctive aspects of multinucleated foreign body giant cells, which enclose round and sharply circumscribed, translucent, nonbirefringent bodies that apparently correspond to the implanted PMMA pearls. In addition, epithelioid cells and a sparse lymphocytic infiltrate were found surrounding these bodies embedded in a loose sclerotic stroma.¹²

Similar histologic findings were detected in the biopsy specimen of our patient's forehead (**Figure 2**). In addition, the ultrastructural examination revealed microspheres within the cytoplasm of giant cells and smaller particles within the macrophages, which led to the supposition of degradation (**Figure 3**). The histologic and

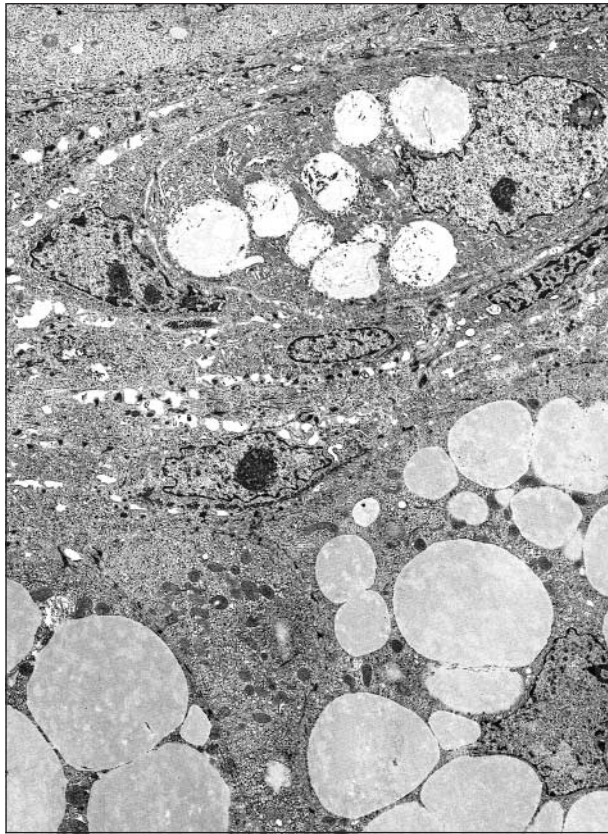


Figure 3. Ultrastructural findings of amorphous polymethylmethacrylate microspheres within macrophages in deep layers of the dermis (original magnification $\times 1600$).

ultrastructural alterations were detected in the middle and lower dermis as well as in deeper layers of the subcutis.

Several explanations for the occurrence of these nodules have been considered, but the exact reason for a granulomatous host response is still unknown. Some authors interpret foreign body granulomas as a low-grade chronic inflammation in the sense of a usual second response to implantation, which would be clinically invisible after strictly subdermal injection and only accidentally diagnosed by histologic examination.^{12,13} In addition, superficial intradermal implantation itself may lead to granulomas.^{2,3} Furthermore, undesired dislocation of the subdermally localized implant to more superficial skin parts—especially of the forehead because of its frequent muscle movement—should be discussed. Investigations of intradermal models of guinea pigs demonstrated transepidermal elimination that began as a movement of the PMMA beads toward the epidermis.³ Particle size analyses in the same study indicated that some of the PMMA particles were smaller than 35 μm in diameter and consequently susceptible to phagocytosis and migration. The presumption that degradation of the microspheres due to local enzymatic activity or aggressive metabolites causes foreign body granulomas requires further, predominantly long-term, investigations. In addition, there may be a correlation between the quantity of the implanted material and the incidence of foreign body granulomas, as also reported for augmentation with silicone fluid.^{14,15}

Even if true granuloma formation after implantation of PMMA is not very frequent, a reliable and easily

Editorial Comment: The authors should be commended for their innovative use of allopurinol to treat their patient's granulomatous reaction secondary to injections of PMMA microspheres. Although it is theorized that allopurinol may act as a catalyst in the formation of superoxides or act as a free radical scavenger, the exact mechanism of action is not known. Allopurinol is generally well tolerated and relatively inexpensive, and it provided this patient with relief of symptoms while allowing her to maintain her cosmetic improvement. With the increasing popularity of temporary and permanent filler agents, and more agents on the market, it is plausible that we will see an increased number of such reactions. This article should stimulate the trial of drugs such as allopurinol in other granulomatous reactions for dermatologists and cosmetic surgeons alike.

Dee Anna Glaser, MD

tolerated treatment is urgently needed. Intralesional injection of long-lasting crystalline corticosteroid usually has been the treatment of choice,¹⁶ but severe granulomas occasionally require surgical excision. Application of corticosteroid cream was recommended for treatment of early inflammatory reactions after too superficial implantation.¹⁶ However, these treatment options could lead to disfiguration by skin atrophy or scarring.

Allopurinol is widely used for the treatment of hyperuricemia, but also several case reports within the past 2 decades describe beneficial effects in patients with cutaneous sarcoidosis, even with histologically confirmed scar sarcoidosis.¹⁷⁻²¹ The exact mode of action in cases of sarcoidosis is still unclear. However, it is well known that allopurinol is an inhibitor of xanthine oxidase, a catalyst in the formation of superoxide. Consequently, allopurinol and its metabolite, oxypurinol, act as free radical scavengers. Free radicals are supposed to play an important role in the pathogenesis of granulomatous diseases, and the reduction of their amount could be the key to the therapeutic benefit of allopurinol.²²

Based on the similarities between sarcoidosis and foreign body granulomas,²³ our patient was treated with allopurinol, which was, according to literature, never given for this special indication before. Significant improvement occurred after a 6 weeks of treatment, and almost complete regression was seen about 16 weeks after starting the treatment. Because of its impressive positive effect, allopurinol can be recommended as therapy for foreign body granulomas; it eliminates the need for painful intralesional corticosteroid suspension injections and avoids disfiguration due to excision.

Accepted for publication January 29, 2002.

Corresponding author: Wilhelm Stolz, MD, Department of Dermatology, University of Regensburg, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany (e-mail: wilhelm.stolz@klinik.uni-regensburg.de).

REFERENCES

1. Lemperle G, Ott H, Charrier U, Hecker J, Lemperle M. PMMA microspheres for intradermal implantation, I: animal research. *Ann Plast Surg.* 1991;26:57-63.
2. Lemperle G, Hazan-Gauthier N, Lemperle M. PMMA microspheres (Artecoll) for skin and soft tissue augmentation, II: clinical investigations. *Plast Reconstr Surg.* 1995;96:627-634.
3. McClelland M, Egbert B, Hanko V, Berg RA, DeLustro F. Evaluation of Artecoll polymethylmethacrylate implant for soft tissue augmentation: biocompatibility and chemical characterization. *Plast Reconstr Surg.* 1997;100:1466-1474.
4. Wiest L, Landthaler M, Stolz W. Hautaugmentation mit Polymethyl-methacrylat (Artecoll). In: Konz B, Wörle B, Sander CA, eds. *Ästhetische und korrektive Dermatologie.* Berlin, Germany: Blackwell Wiss Verlag; 1998:196-202.
5. Lemperle G, Cohen SR, Holmes RE. Biocompatibility of injectable microparticles. Paper presented at: 31st Annual Meeting of the Association of German Plastic Surgeons; October 13, 2000; Magdeburg, Germany.
6. Henze U, Zwadlo-Klarwasser G, Klosterhalfen B, Höcker H, Richter H, Mittermayer C. Kunststoffe für den medizinischen Einsatz als Implantatmaterialien. *Dtsch Arztebl.* 1999;96:979-986.
7. Maas CS, Papel ID, Greene D, Stoker DA. Complications of injectable synthetic polymers in facial augmentation. *Dermatol Surg.* 1997;23:871-877.
8. Roberts J, Quastel JH. Particle uptake by polymorphonuclear leucocytes and Ehrlich ascites-carcinoma cells. *Biochem J.* 1963;89:150.
9. Prätten MK, Lloyd JB. Pinocytosis and phagocytosis: the effect of a particulate substrate on its mode of capture by rat peritoneal macrophages cultured in vitro. *Biochem Biophys Acta.* 1986;881:307-313.
10. Mang WL, Sawatzki K. Fremdkörperreaktion nach Implantation von PMMA (Polymethylmethacrylat) zur Weichteilaugmentation. *Zeitschr Hautkr.* 1998;73:42-44.
11. Hoffmann C, Schuller-Petrovic S, Soyer HP, Kerl H. Adverse reactions after cosmetic lip augmentation with permanent biologically inert implant materials. *J Am Acad Dermatol.* 1999;40:100-102.
12. Rudolph CM, Soyer HP, Schuller-Petrovic S, Kerl H. Foreign body granulomas due to injectable aesthetic microimplants. *Am J Surg Pathol.* 1999;23:113-117.
13. Allen O. Response to subdermal implantation of textured microimplants in humans. *Aesthetic Plast Surg.* 1992;16:227-230.
14. Webster RC, Gaunt JM, Hamdan US, Fuleihan NS, Smith RC. Injectable silicone for facial soft tissue augmentation. *Arch Otolaryngol Head Neck Surg.* 1986;112:290-296.
15. Wilkie DA. Repair of superior palpebral defect in a horse by use of silicone subdermal implant. *J Am Vet Med Assoc.* 1992;15:821-824.
16. Lemperle G, Romano JJ, Busso M. Soft tissue augmentation with Artecoll: 10-year history, indications, technique and potential side effects. Paper presented at: the 27th Annual Meeting of the Canadian Society of Aesthetic (Cosmetic) Plastic Surgery; September 8-9, 2000; Montreal, Quebec.
17. Pollock JL. Sarcoidosis responding to allopurinol. *Arch Dermatol.* 1980;116:273-274.
18. Samuel M, Allen GE, McMillan SC, Burrows D, Corbett JR, Beare JM. Sarcoidosis: initial results on 6 patients treated with allopurinol. *Br J Dermatol.* 1984;111:20.
19. Brechtel B, Haas N, Henz BM, Kolde G. Allopurinol: a therapeutic alternative for disseminated cutaneous sarcoidosis. *Br J Dermatol.* 1996;135:307-309.
20. Voelter-Mahlknecht S, Benez S, Fierbeck G. Treatment of subcutaneous sarcoidosis with allopurinol. *Arch Dermatol.* 1999;135:1560-1561.
21. Pfau A, Stolz W, Karrer S, Szeimies RM, Landthaler M. Allopurinol in der Behandlung der kutanen Sarkoidose. *Hautarzt.* 1998;49:216-218.
22. Picard Ami LA, MacKay A, Kerrigan CL. Effect of allopurinol on the survival of experimental pig flaps. *Plast Reconstr Surg.* 1980;89:1098-1103.
23. Payne R, Thomas M, Black MM. From silica granuloma to scar sarcoidosis. *Clin Exp Dermatol.* 1983;8:171-175.

Submissions

Clinicians, local and regional societies, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Submit 4 double-spaced copies of the manuscript with right margins nonjustified and 4 sets of the illustrations. Photomicrographs and illustrations must be clear and submitted as positive color transparencies (35-mm slides) or black-and-white prints. Do not submit color prints unless accompanied by original transparencies. Material should be accompanied by the required copyright transfer statement, as noted in "Instructions for Authors." Material for this section should be submitted to George J. Hruza, MD, Laser and Dermatologic Surgery Center Inc, 14377 Woodlake Dr, Suite 111, St Louis, MO 63017.