Foreign Body Granulomas Caused by Polymethylmethacrylate Microspheres

Successful Treatment With Allopurinol

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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

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...
be detected, and their density increased until the fourth ent. At this time, the first autologous collagen fibers could spheres into clusters, and vascularization became appar-

strands formed compartments dividing the micro-

the entire implant. After 2 to 3 weeks, connective tissue thoroughly invaded the implant. Within the following 6 

days, monocytes differentiated to fibroblasts. Nine days 

after the implantation, the microspheres were totally cov-

red by human fibroblasts and collagen fibers. It is calculated that approximately 50% of the Artecoll implant remains). This combination leads to the persistent aesthetic result.

Nowadays, several alloplastic or autologous materials are available for the treatment of wrinkles and other soft tis-

sue 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 

collagen solution is used as a carrier and represents 75%

of synthetic implants with irregular surface characteris-

tics. On the other hand, it is assumed that PMMA mi-

croospheres cannot be phagocytized or removed, and the 

material is believed to be permanently deposited be-

cause 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 ad-

verse effects such as painful and disfiguring granuloma-

tous skin lesions weeks or even years after implantation 

of PMMA microspheres.10-12 According to these case re-
pports, unsatisfactory cosmetic effects or visible, painful 

nODULES led to excision of the material. Subsequent hist-

opathologic and ultrastructural examination showed the 
distinctive aspects of multinucleated foreign body giant 
cells, which enclose round and sharply circumscribed, 

translucent, nonbirefringent bodies that apparently cor-

respond to the implanted PMMA pearls. In addition, epidermal 
cells and a sparse lymphocytic infiltrate were found surrounding these bodies embedded in a loose sclero-
ctic 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 sup-

position of degradation (Figure 3). The histologic and

Figure 2. Granulomatous infiltrate with numerous multinucleate giant cells, histiocytes, and lymphocytes surrounding apparently empty cystic structures (hematoxylin-eosin; original magnification ×100).
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. In addition, superficial intradermal implantation itself may lead to granulomas. Furthermore, undesired dislocation of the subdernally 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. 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.

Even if true granuloma formation after implantation of PMMA is not very frequent, a reliable and easily tolerated treatment is urgently needed. Intrallesional injection of long-lasting crystalline corticosteroid usually has been the treatment of choice, but severe granulomas occasionally require surgical excision. Application of corticosteroid cream was recommended for treatment of early inflammatory reactions after too superficial implantation. 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. 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.

Based on the similarities between sarcoidosis and foreign body granulomas, 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 intrallesional corticosteroid suspension injections and avoids disfiguration due to excision.

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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
REFERENCES


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.