

## Review Article

# Foreign Body Granulomas: Silicone as a Model (A Review of Clinical Manifestation, Histology, Pathophysiology and Treatment)

Ebrahim Mirakhor<sup>1\*</sup>, David M Duffy<sup>2</sup>

<sup>1</sup>Resident Physician, Los Angeles, CA, USA

<sup>2</sup>Dermatologist, Los Angeles, CA, USA

\*Corresponding author: Ebrahim Mirakhor, Resident Physician, 8700 Beverly Blvd #5512, Los Angeles, CA-90048, USA. Tel: +13106910048; Email: ebrahimirakhor@yahoo.com

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## Introduction

With the rampant permeation of idealized beauty standards and desire for everlasting youth, a revolution in cosmetic medicine has occurred. Although, surgical procedures historically dominated the cosmetic stratosphere, many have been supplanted by their less invasive counterparts, namely biotoxins and injectable filler [1-4]. According to American Society of Dermatologic Surgery procedure survey, between 2005 and 2007 soft tissue augmentation procedures have increased by 130 percent [5,6]. Additionally, with increased life-expectancy and growing utilization of fillers for alternative purposes (e.g. HIV-associated lipodystrophy), the demand for these procedures will certainly continue to rise [4,7]. Although generally considered safe, the use of various fillers can result in severe complications ranging in incidence between 1:80 to 1:50000 [8-11].

Complications are broadly divided into short-term (pain, swelling, infection, immediate hypersensitivity, ecchymosis, embolization, amaurosis, necrosis, herpes reactivation, nerve paralysis), mid-term (ulceration, granulomatous reactions, nodule formation), and long-term (delayed hypersensitivity, migration) events [4,6,8, 11-14]. Among these, Foreign Body Granulomas (FBG) have piqued the curiosity of many given the associated dreaded physical and psychological impact on patients as well as medicolegal implications for practitioners performing them [2,11,15,16]. Herein, we aim to review the clinical manifestation of silicone granulomas, examine possible pathophysiologic mechanisms underlying their formation, and discuss therapeutic strategies.

## Historical Perspective

Injectable silicone had its inception in the 1940's Europe and was mainly employed to improve body contours. By the late

1950s, silicone had made its U.S. debut and received a short-lived FDA approval in early 1960s for soft-tissue augmentation, however exploitation of pure and adulterated silicone in large volumes resulting in disfiguring complications led to the 1964 legislation criminalizing its use [3,9,17-19]. Despite this ban, over the ensuing forty years silicone continued to be used for correction of rhytides, diabetic foot disease, scar revisions, and rhinoplastic defects [20-23]. Currently Adotosil 5000 and Silikon 1000 have FDA approval for treatment of retinal detachment but under the Modernization Act of 1997, the off-label cosmetic potential of these products has been harnessed especially when more permanent results are desired [9,16,24-26].

Based on decades of scientific experience with liquid silicone, successful clinical outcome is correlated with purity of the product, proper administration technique, and most importantly the volume of injected silicone [3,9-11,19, 27,28]. Other less significant factors associated with long-term complications of various tissue-fillers, like granuloma formation include: number of repeated injections, filler particle size, charge, surface smoothness, and hydrophilicity [15,17,29,30].

Many competing theories about the evolution of foreign body granulomas have been proposed but now it is widely accepted that immune-mediated reactions underlie their formation [18,22,31,32]. It is postulated that infections at distant sites, e.g. dental abscesses or sinusitis, may serve as the trigger setting off an immune domino effect leading to a granulomatous response; this is in part supported by reports of symptomatic improvement after treatment with antibiotics [3,17,18,26,32]. Comparable theories have suggested, biofilms covering silicone microdroplets introduced during filler injection or deposited via bacteremic seeding, may serve as a nidus of dormant infection and elicit a delayed granulomatous response

when the organisms are reactivated [4,18,33].

## Clinical Manifestation

Winer et al coined the term “Siliconoma” in 1964 and was the first person to recognize their formation following injection of adulterated silicone [17,34]. Subsequently, many more cases have been reported and although rare, the incidence of true foreign body granulomas is estimated at 0.01 to 1% [35]. Granulomas are now categorized as mid to long term complications of silicone and can occur as early as a few months to as late as a few decades after injection [15,17,33,36-40]. They clinically manifest as intermittent to persistent swelling with associated induration, erythema, and purple discoloration [15,17]. Although many occur in asymptomatic individuals, associated precipitants include consumption of alcohol, exercise, sunburns, bacterial or viral infections, and exposure to allergens [11,16-18].

While unequivocal diagnosis of a silicone granuloma is histologic, its recognition and differentiation from a nodule remains principally clinical in nature. Nodules must always be considered on the differential but can often be easily ruled out based on clinical characteristics.

Nodules occur secondary to technical errors when fillers are implanted too superficially and become visually evident within weeks of injection. They present as a single lump at the original injection site, are whiter in coloration, have a firm consistency owing to less cellular elements, and most importantly do not grow in size. Moreover, response to intralesional corticosteroids is limited given the lack of cellular reaction. They are best treated by excision [3,10,11,15,22].

In contrast, foreign body granulomas differ in time course, with involvement of multiple injected loci in close temporal proximity, and display intermittent flare-ups and regressions. The presence of cellular elements allows for a more rubbery consistency, prolonged congestion of dermal capillaries endow a bluish hue to the surrounding area, and most importantly granulomas grow in size and do respond to intralesional steroids [3,9,10,15,17,22].

## Histopathology

Granulomas are simplistically the body’s attempt to siege and eliminate invading agents and may complicate any foreign body implantation [13,35-37,39,41-53]. Histologically, granulomas are characterized by an inflammatory infiltrate consisting of histiocytes, macrophages, multinucleated giant cells, epithelioid cells and varying proportion of lymphocytes, plasma cells, neutrophils, and eosinophils [3,15,17,54]. The actual histologic cellular composition of a granuloma differs based on the filler material used and can exist on a continuum of Cystic, Edematous, and Sclerosing patterns with the edematous granuloma pattern being most frequently linked to injectable silicone [3,8,14,15,22,42,43,55-62]. The edematous pattern, also known as lipogranuloma or Swiss-

Cheese pattern, shows diffuse 1-30  $\mu\text{m}$  silicone vacuoles with a predominance of lymphocytes and macrophages, some plasma cells, and scattered giant cells [3, 15,22,56,58].

Regrettably, the absence of dermal filler-induced FBGs in modern pathology texts and literature leads to many histopathologists misclassifying the normal foreign body reaction as a FBG [3,55,63]. It is imperative to note, that the initial post-implantation influx of mononuclear cells and scattered giants’ cells is a deliberate response to presence of foreign material and will extinguish within a few weeks resulting in a stable histologic picture [3,4, 32 64].

## Pathophysiology

The exact pathophysiologic mechanism of silicone granuloma formation has not yet been elucidated and any discussion of plausible theories necessitates understanding of the natural host immune response to implanted foreign material. Simplistically, silicone is a fibroplastic filler, hence its mechanism of augmentation is twofold: Gross displacement and fibroplasia. Injected silicone causes displacement of subcutaneous tissue and consequently, the influx of neutrophils and macrophages orchestrate a localized inflammatory reaction followed by fibroblast deposition of collagen to anchor the filler material in place [18,65,66]. This is why defects are intentionally under corrected with silicone and require multiple treatment sessions in order to achieve the desired outcome and avoid overcorrection as fibroplasia occurs.

More mechanistically, the physiologic response to foreign body implantation can be divided into 5 phases: recognition, adsorption of plasma proteins, macrophage recruitment, fusion to form multinucleated giant cells, and crosstalk [15,67]. Immediately after implantation, the body recognizes tissue injury and promotes infiltration of neutrophils into the microenvironment. Concomitantly, plasma proteins like fibrinogen, fibronectin, vitronectin,  $\gamma$ -globulins, complements and coagulations factors adhere to the surface of the injected filler and form a provisional matrix [15,29,67-69]. The newly formed matrix releases chemoattractant like Interleukin (IL-1) to direct monocyte extravasation/migration to the injured site. Maturation of monocytes into macrophages and the differential interaction of surface protein and integrin receptors leads to adherence of macrophages onto the provisional matrix. This interaction in turn promotes the release of tumor necrosis factor (TNF- $\alpha$ ), IL-6, and Granulocyte Colony Stimulating Factors (G-CSF) which recruits additional macrophages to the area. Presence of IL-4 and IL-13 cause upregulation of mannose receptors on macrophage extensions and mediates fusion into Giant cells in order to augment phagocytic abilities [15,70]. Cross talk between macrophages will dictate whether further recruitment of mononuclear cells is warranted or if the immune response can safely be mitigated. Normally the latter is favored with macrophages releasing fibrogenic cytokines to stabilize the injected area [67,71,72].

Granulomas form months to years after immune quiescence; an unknown trigger reactivates dormant local macrophages lead-

ing to recruitment of CD4+ T-lymphocytes via antigen presentation and stimulates release of higher-than-normal concentrations of cytokines like TNF- $\alpha$  facilitating the formation of granulomas [73]. In fact, the failure of TNF $\alpha$ -deficient mice to mount a granulomatous response and inability of wild-type mice to maintain granulomas after administration of TNF- $\alpha$  blockers, supports this notion [74]. The key role of radicalized T-cells and excess TNF- $\alpha$  in formation of silicone granuloma, in many ways, resembles the immunopathologic pathway implicated in sarcoidosis and has been reinforced by successful treatment of silicone granulomas using TNF- $\alpha$  inhibitors [73,75,76]. Moreover, hypercalcemia secondary to silicone granulomas and resolution with systemic steroids further mirrors sarcoidosis and points to a shared immune mechanism [36,77,78]. Finally, development of silicone granulomas following interferon therapy in hepatitis C infected individuals further incriminates the adaptive branch of the immune system in evolution of these granulomas [35,79].

What are the triggers of this granulomatous response? As discussed above, the historical use of adulterated silicone fueled speculations that microbial contaminants, fibroblastic agents, bacterial infections, and biofilms elicited an amplified immune response causing granulomas to form [18,22,32]. Despite the advent of sterile products and microdroplet technique, silicone granulomas continue to occur forcing newer theories to shift focus onto alternate sources like the "Provisional matrix." While silicone itself is thought to be inert, its interaction with in-vivo surface proteins may be immunogenic and instigate a granulomatous response [17,18,31]. For example, fibrinogen undergoes conformational change when attached to silicone, displaying 2 previously hidden epitopes that are able to induce an inflammatory response [80]. Fibrinogen is one of many surface proteins that may play a key role in igniting a granulomatous response. Although less likely, enzymatic degradation of Silicone to Silica, a known cause of granuloma formation should also be entertained [81,82]. Presence of genetic predispositions in foreign body processing and immune regulation may also play a role in FBG formation but has not been clearly addressed thus far.

## Prevention and Treatment

To avoid complications of silicone, a few precautionary measures should be noted. First line of defense is prevention of complications and begins with choosing the right patient, who understands the off-label use of silicone, the need for multiple injections, and its delayed but often permanent results. Injection should be avoided in individuals with chronic sinusitis, dental caries, acne, or other active infections as well as in those predisposed to facial trauma [11,17,18]. Patients receiving interferon therapy should also avoid filler augmentation for reasons described previously [79]. Injection into the eyelids, horizontal creases of forehead and philtrum, breasts, and bound-down scars is contraindicated [16,17,26,83]. Discontinuation of antiplatelets and anticoagulants

along with pre- and post-application of ice-packs helps minimize swelling and bruising [11,17,84]. Second line of defense is administration of small quantities of FDA approved silicone products under sterile conditions by practitioners trained in the microdroplet technique [16-18,22,25,85].

Once granulomas have formed, the mainstay of treatment is intralesional steroids like Triamcinolone (20-40 mg/ml) every 2 to 4 weeks [50,53,86]. Addition of 5-fluorouracil or bleomycin to intralesional steroid can be employed in refractory cases with good response owing to their antimetabolite function limiting further proliferation of fibroblasts and immune cells [15,35]. This combination requires less steroid and thereby reduces steroid related side effects like atrophy and telengectasias [87].

In treatment resistant and recurrent granulomas, systemic therapy with oral prednisone at 30 mg/day with a prolonged taper is recommended [3,11,15,18,32]. Additionally, treatment with broad-spectrum oral antibiotics like minocycline and tetracycline is reasonable as the antibacterial properties helps eradicate infections/biofilms while their anti-inflammatory properties promote immune down regulation [50,88,89]. Along similar lines, allopurinol 300 mg daily has resulted in enduring treatment of silicone granulomas via speculated free radical scavenging properties of the drug [39,90]. Finally, TNF- $\alpha$  antagonists like etanercept (50 mg twice weekly) hold great promise in treatment of silicone granulomas, owing to their ability to render TNF- $\alpha$  less effective thus modulating the T-cell response that lies at the heart of granuloma formation, as initially proposed by Duffy [75,76,91].

While generally discouraged, surgical options remain a treatment of last resort. More localized and well-defined granulomas can be surgically excised with good outcomes, while those with irregular borders tend to recur even after excision [15,17,18]. Dermabrasion can be considered a novel therapeutic strategy for diffuse silicone granulomas but is plagued by need for multiple attempts and a protracted healing course [86]. Extensive cases may ultimately require fat graft or flap reconstruction [15,36,37].

## Conclusion

While silicone possesses many characteristics of an ideal filler, the use of adulterated products masquerading as silicone between 1960-1990s and a myriad of anecdotal reports highlighting its complications have created an environment of mistrust. Although, trials plagued by methodological flaws and inadequate follow-up have further intensified our uncertainties about silicone, recent well-designed rigorously controlled trials with highly purified products employing the microdroplet technique have begun and demonstrate acceptable safety and efficacy. Further investigation to unveil the pathophysiology of silicone granulomasis warranted and will undoubtedly help in identification of host predispositions, immune triggers, and shed light on more novel therapeutic strategies.

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