

Silicone Gel-Filled Breast Implants: Is Local Inflammation Associated With Fat Necrosis?

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■ **Abstract:** Granuloma formation and chronic inflammation are local reactions that are associated with implantation of medical grade silicone. These responses lead to capsular contraction, pain, and cosmetic problems. In addition, there have been a few reports of connective tissue disease in patients with silicone gel-filled implants. The purpose of this paper is to raise the possibility that local responses to silicone gel-filled implants are mediated by fat necrosis.

Results of histologic findings and patient records in six patients indicate that patients experiencing implant leakage or failure exhibited classic signs of a foreign-body response, including the presence of giant cells and foamy macrophages. Most of the observed vacuoles were empty and appeared similar to enucleated fat cells, although some contained foreign material. These observations suggest that the physical presence or degradation products of the implants may have elicited fat cell necrosis that contributed to the chronic inflammatory response. In contrast,

patients with intact implants showed no signs of a chronic foreign-body response. None of the patients in this study demonstrated any systemic complications.

It is concluded that although there have been numerous reports of empty vacuoles containing silicone that are either derived from the membrane that surrounds the implant or from the gel, there are no reports linking these vacuoles to the vacuoles seen in fat tissue necrosis, even though histologically the two processes are morphologically similar. Therefore, it is important to ask whether some of the adverse reactions observed with silicone gel-filled implants may be mediated via fat cell necrosis. ■

Complications associated with silicone implants have been well documented since the 1970s. Local complications associated with the use of breast implants include asymmetry, fibrous capsule formation, calcification of the fibrous capsule, capsular contraction, excessive hardness, extrusion of the implant, implant deflation, implant displacement, infection, numbness, postoperative lactation, leakage, sensitization, interference with cancer detection, potential for cancer, and visible and palpable prostheses (1, 2). Systemic reactions associated

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with silicone breast implants include scleroderma, systemic lupus erythematosus, rheumatoid arthritis, Sjogren syndrome, and connective tissue disease (3-7).

Local adverse reactions include chronic inflammation and granuloma formation, which is part of a non-specific immunologic response to medical grade silicone (6). This response is associated with the recruitment of macrophages at the implant interface (8) such that they become embedded within the implant (9). Liquid silicone has been identified away from the site of the implant within macrophages (10). The presence of liquid and particulate silicone in the spaces around the implant has been associated with giant cell and granuloma formation (11-16).

Less numerous are the reports of connective tissue or autoimmune disease in patients who previously received a silicone implant. These reports include the development of systemic sclerosis (scleroderma) after augmentation mammoplasty (17, 18) or alloplastic chin implantation (18). Another report (19) concluded that most women with silicone breast implants have normal results on common immunologic tests. However, some women had findings that were unusual even for patients referred to rheumatologists. A recent report (20) indicated that 35% of women with silicone breast implants have antibodies to human native and denatured types I and II collagens. This number is higher than observed in any other autoimmune disease and is similar to that seen in chronic erosive rheumatoid arthritis. However, Gabriel et al (21) recently reported that they found no association between breast implants and connective tissue diseases.

The purpose of this paper is to review the histopathology of tissues from six patients receiving silicone gel-filled implants and to present the hypothesis that local inflammatory responses to implants are mediated via fat necrosis.

CLINICAL STUDIES

Biopsies of the capsular tissue surrounding breast implants were performed as part of the routine pathologic evaluation associated with revision surgery on six patients (Table 1) who previously received silicone gel-filled implants. The patients ranged in age from 39 to 59, with implants that had been in place from 8 to 17 years. Three of the patients experienced either implant leakage or rupture, while the other patients had local complications involving capsular contraction. None of the patients experienced any systemic complications such as joint pain or swelling.

All biopsies were processed after fixation using procedures for dehydration through a graded series of alcohols,

Table 1. Histories of Patients Undergoing Mammoplasty Revision Surgery

Patient	Age (yrs)	Implant Age (yrs)	Symptoms
1	39	15	Bilateral leakage, asymptomatic
2	59	8	Rupture, asymptomatic (subpectoral)
3	46	?	Asymptomatic (subpectoral)
4	44	17	Pain, severe capsular hardness (subpectoral)
5	44	?	Severe capsular contraction, cosmetic deformities
6	45	17	Rupture of right prosthesis, asymptomatic

embedding in paraffin, sectioning, and staining with hematoxylin and eosin.

RESULTS

All tissues examined were primarily composed of either scar or muscle tissue, depending on whether the implants were placed subcutaneously or beneath the muscle, respectively (Table 2). In sections where scar tissue (capsule) predominated, ducts, occasional hair follicles, and sebaceous glands could be seen. In patients in whom leakage or rupture of the implant was noted (patient numbers 1, 2 and 6), vacuoles of various sizes could be seen throughout the fibrous scar tissue (Fig. 1a). In some cases these vacuoles contained refractile particles (Fig. 1b); in other cases they were filled with a fibrous material or they appeared empty (Fig. 1c). The vacuoles appeared to form at or near giant cells that were surrounding foreign debris. In some areas vacuoles appeared to fuse with other vacuoles to form larger structures. Fibrous tissue appeared to be laid down between the vacuoles.

Table 2. Histopathology of Capsule Surrounding Breast Implant

Patient	Observations
1	Vacuoles containing foreign refractile material (presumably debris from implant), empty vacuoles, foamy macrophages, some foreign body giant cells, fibrous scar tissue and some remaining ductal tissue
2	Fibrous scar tissue, muscle and fat
3	A few vacuoles, fibrous scar tissue, foamy macrophages, refractile inclusions, giant cells
4	Muscle, fat, fibrous scar tissue
5	Fat, ductal tissue, fibrous scar tissue
6	Extensive vacuolization (swiss cheese appearance), refractile particles, giant cells, granulomatous reaction, fibrous scar tissue



Figure 1. Low (a), medium (b) and high power (c) view of histologic section from patient 6. Low power view (a) shows extensive vacuolization (swiss cheese appearance) of tissue surrounding implant (not shown). Medium power view (b) shows vacuoles containing foreign material (arrows). High power view (c) shows refractile particles of foreign material (arrows) and foreign-body giant cells (gc).

Other areas were filled with large dilated macrophages that had cytoplasm filled with foreign material (foamy macrophages). There did not seem to be any obvious relationship between the appearance of vacuoles and the location of foamy macrophages. However, both of these observations were associated with gel-filled implants that leaked silicone. Vacuoles were not observed in patients with intact implants.

DISCUSSION

It has been known for several decades that silicone gel will bleed (diffuse) through the polymeric membrane into the surrounding tissues (23), leading to phagocytosis, foamy macrophage formation, and granulomas. The silicone bleed has been reduced by substituting larger groups for methyl groups on silicone (22). The amount of silicone bleed into the capsule is reported to be directly associated with the degree of capsular contraction (24, 25).

The long-term follow-up of patients with silicone breast implants includes watching for capsular contraction associated with capsule formation around gel-filled implants. Clinically this led to a rubbery firmness of the breast often associated with a visible distortion (22). This condition resulted from a spherical contraction of the implant by the surrounding fibrous tissue. Patients in one study undergoing surgery to remove the capsule and release the contracture exhibited evidence of a chronic inflammatory infiltrate surrounding the implant and vacuolated spaces apparently containing a foreign material (23). Foreign-body giant cells were also occasionally seen, with droplets of foreign material in vacuoles identified as poly(dimethyl siloxane) (26).

Foreign-body responses to silicone implant wear particles have been noted previously (26–29). This reaction has been termed a “benign foreign-body giant cell” response to local wear particles, since no silicone particles or giant cells were found in any distant organs (26). However, in a recent study, cell viability was significantly decreased on silicone and polyurethane textured surfaces, leading the authors to hypothesize that normal cellular functions are altered in response to prosthetic surfaces resulting in exaggerated soft tissue responses (30).

During the course of our study we observed “vacuoles” only in patients in whom implant rupture or leakage was observed. Leakage led to either foamy macrophage or giant cell formation in the vicinity of the vacuoles. Neither event was associated with any systemic effects in the patients studied. After careful review of the histopathology observed in patients with silicone-gel leakage, it was con-

cluded that the morphology of the tissue was similar to that reported for breast fat tissue necrosis.

Fat tissue necrosis of the breast is usually associated with a history of trauma. The lesion initially consists of necrosis of adipocytes and hemorrhage due to mechanical trauma. Subsequently, inflammatory cells engulf lipid debris. As the process resolves, there may be marked fibroblast proliferation, granuloma formation, and fibrous scar tissue deposition (31).

It is interesting to consider whether the chronic inflammatory response observed in patients with ruptured implants is in part a result of fat tissue necrosis. In the case of fat tissue, neutrophils may accumulate among the injured fat cells and activate lymphocytes, causing further macrophage infiltration and scar tissue formation possibly through release of lymphokines (Fig. 2). Fat can also excite a granulomatous reaction through differentiation of macrophages to multinucleated macrophages and giant cells.

It is possible, based on these observations, to hypothesize that capsular contraction may be a healing response that is stimulated by chronic inflammation associated with implant rupture and the resulting fat necrosis. The chronic inflammation that goes on initiates a cycle of macrophage

phagocytosis of silicone or necrotic fat tissue followed by deposition of fibrous tissue between vacuoles as they are either fused or condensed. In this manner fibrous scar tissue is deposited as the result of either fat tissue necrosis or the presence of silicone, and ultimately contracts as the wound healing proceeds.

In recent years the study of silicone gel-filled implants and their surrounding capsules has been limited by legal issues. Therefore, it has become increasingly difficult to test new hypotheses concerning the pathogenesis of local and systemic complications of silicone gel-filled implants. Although silicone gel-filled implants have been used both in the breast as well as in the face, adverse reactions have been reported primarily with breast implants. Consistent with this information is our observation that local inflammation associated with rupture of silicone gel-filled implants appears histologically identical to fat tissue necrosis of the breast. In both cases empty vacuoles, granulomas, and resulting deposition of scar tissue are observed. Therefore, it seems plausible that the adverse reactions associated with silicone gel-filled implants are partially mediated through the effect of silicone gel on fat tissue. Fat tissue necrosis may be promoted in the presence of silicone gel, triggering an inflammatory response.

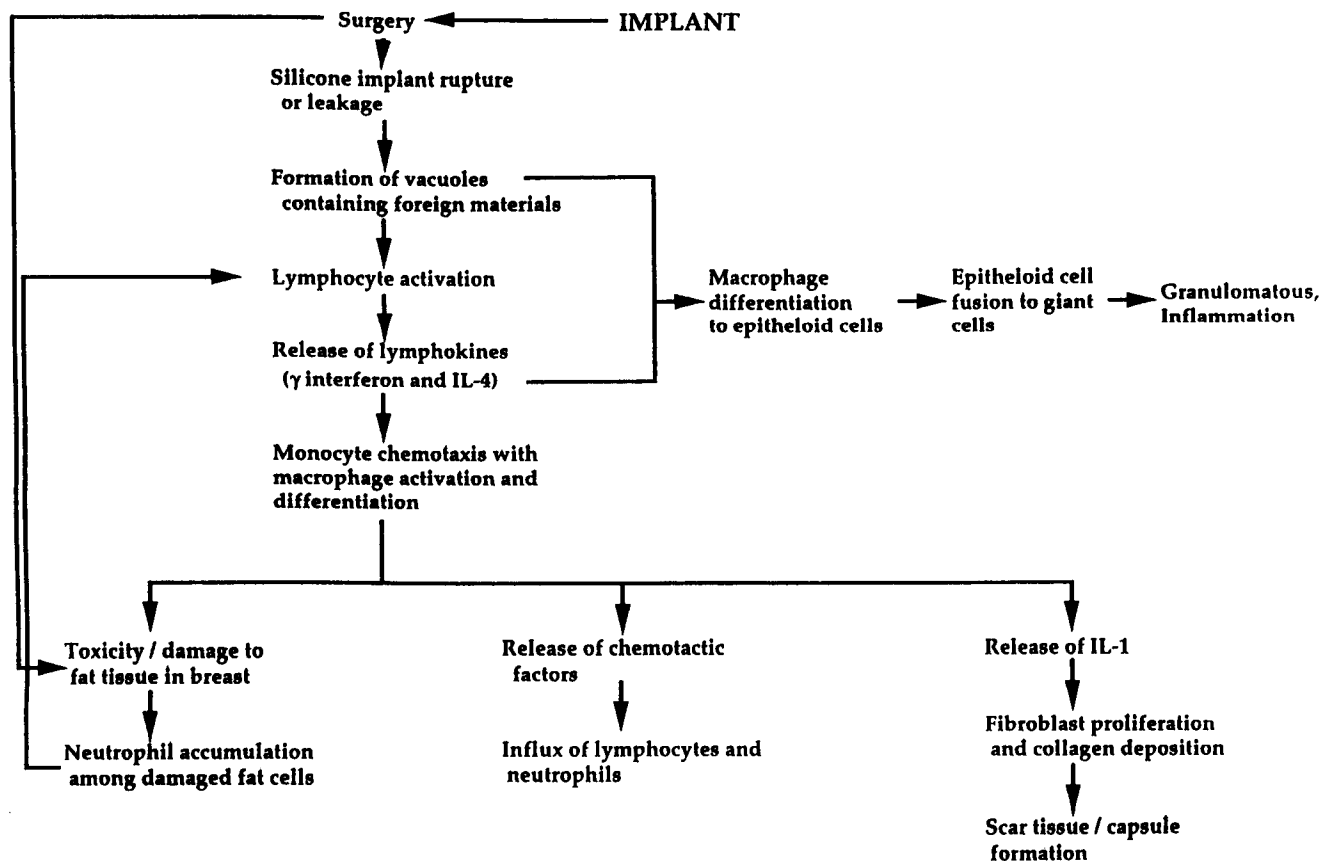


Figure 2. Diagram of how implant rupture may lead to fat tissue necrosis by lymphocyte activation and release of lymphokines.

Injectable silicone has been used in the face for decades, with adverse reactions associated only with impurities and improper injection techniques. This is also consistent with the fact that silicone is normally injected intradermally and not directly into fat. These observations point to the possible adverse effects of silicone gel on fatty tissue.

Although we have limited data on the numbers of patients experiencing implant rupture and histological responses typical of fat necrosis, it is our hope that other workers in the field may be able to provide additional evidence to support or refute this hypothesis. If our hypothesis is found to be correct, it will then be important to elucidate the mechanism by which placement of silicone gel-filled implants in sites with large amounts of fat generate adverse responses.

REFERENCES

- McGrath MH, Burkhardt BR. The safety and efficacy of breast implants for augmentation mammoplasty. *Plast Reconstr Surg* 1984;74:550-60.
- Berkowitz F, and Elam MV. Augmentation mammoplasty: 20 years of clinical experience. *Am J Cosmetic Surg* 1985;2:48-66.
- Van Nunen SA, Gatenby PA, Basten A. Post-mammoplasty connective tissue disease. *Arthritis Rheum* 1982;25:694-97.
- Kumagai Y, Shiokawa Y, Medsger TA Jr, Rodnar, GP. Clinical spectrum of connective tissue disease after cosmetic surgery. *Arthritis Rheum* 1984;27:1-12.
- Sergott TJ, Limoli J, Baldwin CM, Laub, DR. Human adjuvant disease, possible autoimmune disease after silicone implantation: a review of the literature, case studies, and speculation for the future. *Plast Reconstr Surg* 1986;78:104-14.
- Shons AR, Schubert W. Silicone breast implants and immune disease. *Ann Plast Surg* 1992;28:491-99.
- Spiera H. Scleroderma after silicone augmentation mammoplasty. *JAMA* 1988;260:236-38.
- Gayou RM. A histological comparison of contracted and non-contracted capsules around silicone breast implants. *Plast Reconstr Surg* 1979;63:700-9.
- Kossovsky N, Heggers JP, Parsons RW, Robson MC. Analysis of the surface morphology of recovered silicone mammary prostheses. *Plast Reconstr Surgery* 1983;71:795-802.
- Chastre J, Basset F, Viau F, et al. Acute pneumonitis after subcutaneous injections of silicone in transsexual men. *N Engl J Med* 1983;308:764-67.
- Millard DR, Maisels DO. Silicone granuloma of the skin and subcutaneous tissues. *Am J Surg* 1979;64:252-53.
- Wilkie RF. Late development of granuloma after liquid silicone injections. *Plast Reconstr Surg* 1977;60:179-86.
- Kircher T. Silicone lymphadenopathy: a complication of silicone elastomer finger joint prostheses. *Hum Pathol* 1980;11:240-44.
- Gordon M, Bullough PG. Synovial and osseous inflammation in failed silicone-rubber prostheses: a report of six cases. *J Bone Joint Surg* 1982;64A:581-85.
- Endo LP, Edwards NL, Longley S, Corman LC, Panush RS. Silicone and rheumatic diseases. *Semin Arthritis Rheum* 1987;17:112-18.
- Kossovsky N, Heggers JP, Robson MC. The bioreactivity of silicone. *CRC Critical Reviews in Biocompatibility* 1987;3:53-85.
- Varga J, Schumacher HR, Jimenez SA. Systemic sclerosis after augmentation mammoplasty with silicone implants. *Ann Intern Med* 1989;111:377-83.
- Spiera H, Kerr LD. Scleroderma following silicone implantation: a cumulative experience of 11 cases. *J Rheumatol* 1993;20:958-61.
- Bridges AJ, Conley C, Wang G, Burns DE, Vasey FB. A clinical and immunologic evaluation of women with silicone breast implants and symptoms of rheumatic disease. *Ann Int Med* 1983;118:929-36.
- Vasey FB, Havice DL, Bocanegra TS, Seleznick MJ, Bridgeford PH, Germain BF. Clinical manifestations of fifty women with silicone breast implants and connective tissue disease. *Arthritis Rheum* 1992;35:S212.
- Gabriel SE, O'Fallon WM, Kurland LT, Beard CM, Woods JE, and Melton LJ. Risk of connective-tissue diseases and other disorders after breast implantation. *N Engl J Med* 1994;330:1697-1702.
- Council On Scientific Affairs, American Medical Association. Silicone gel breast implants. *JAMA* 1993;270:2602-8.
- Domanskis EJ, Owsley JQ. Histological investigation of the etiology of capsule contracture following augmentation mammoplasty. *Plast Reconstr Surg* 1976;58:689-93.
- Chiang L, Caldwell E, Reading G, Wray, RC Jr. A comparison of conventional and low-bleed implants in augmentation mammoplasty. *Plast Reconstr Surg* 1992;89:79-72.
- Kessler DA. The basis of the FDA's decision on breast implants. *N Engl J Med* 1992;326:1713-15.
- Rees TD, Ballantyne DL Jr, Hawthorne GA. Silicone fluid research—a follow-up summary. *Plast Reconstr Surg* 1970;46:50-56.
- Swanson AB, Nalbandian RM, Zmugg TJ, et al. Silicone implants in dogs: a ten-year histopathologic study. *Clin Orthop* 1984;184:293-201.
- Baker JL, Levier RR, Spielvogel DE. Positive identification of silicone in human mammary capsular tissue. *Plast Reconstr Surg* 1982;69:56-60.
- Bass SJ, Gastwirth CM, Green R, Knights EM, Weinstock RE. Phagocytosis of Silastic material following Silastic great toe implant. *J Foot Surg* 1978;17:70-72.
- Sank A, Chalabian-Baliozian J, Ertl D, Sherman R, Nimni M, Tuan TL. Cellular responses to silicone and polyurethane prosthetic surfaces. *J Surg Res* 1993;54:12-20.
- Bartow SA. The breast. In: Rubin E, Farber JL (eds). *Pathology, 2nd ed.* Philadelphia: J. B. Lippincott, 1994:978-79.