CHRONOLOGY OF SYSTEMIC DISEASE DEVELOPMENT IN 300 SYMPTOMATIC RECIPIENTS OF SILICONE GEL-FILLED BREAST IMPLANTS

ARTHUR E. BRAWER

Department of Medicine

Division of Rheumatology

Monmouth Medical Center

Long Branch, New Jersey

Aims: *To define the time sequence and incremental evolution of the systemic illness manifested by recipients of silicone gel-filled breast implants.* ***Methods:*** *Three hundred patients who became systemically ill following insertion of silicone gel-filled breast implants were examined. Mean age at the time of implantation was 33 years, and the average silicone gel device exposure spanned 12 3/4 years.* ***Results:*** *The onset of systemic disease began on average 2 1/2 years after implant insertion, occurring as early as two weeks after the implant or as late as 18 years afterwards, with 90% of the entire cohort symptomatic after six years. Implant rupture was not the stimulus for disease onset and preceded systemic illness in only nine patients (3%). Subsequent disease progression developed in an exponential manner, eventually encompassing an average of thirty symptoms and signs per patient. Disease acceleration occurred five to six years from the time of implantation, and coincided with failure of the fibrocollagenous capsule. Implant rupture (214 out of 300) served to exacerbate and aggravate any symptoms and signs that were already present but did not alter the rate of sequential disease progression compared to patients who never experienced rupture.* ***Conclusions****: In this cohort of symptomatic silicone gel breast implant recipients, the chronology of systemic disease development simulated a self-perpetuating runaway catalytic reaction and was uniquely different from the varied and established*

evolutions of spontaneous device-free classical connective tissue diseases. This time sequence of disease progression provides strong supportive evidence for the existence of a novel illness, and also offers rational advice for implant removal based primarily on the length of time of device insertion rather than whether or not implants have undergone rupture.

1. Address all correspondence to: Arthur E. Brawer, M.D., 170 Morris Avenue, Long Branch, NJ 07740. Tel.:(732) 870-3133. Fax: (732) 222-0824.

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4. Disclaimer: Dr. Arthur E. Brawer has examined patients at the request of plaintiffs' attorneys, has received compensation from plaintiffs' attorneys for these examinations, and has testified at depositions and at trial on behalf of plaintiffs involved in silicone gel breast implant litigation.

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INTRODUCTION

Silicone gel-filled breast implants have been implicated by numerous investigators as the cause of a novel systemic illness (Lappe, 1993; Borenstein, 1994; Brawer, 1994; Bridges, 1994; Freundlich et al., 1994; Solomon, 1994a, 1994b; Shoaib et al., 1994; Brautbar et al., 1995; Davis et al., 1995; Lappe, 1995; Mease et al., 1995; Shoaib and Patten, 1995; Vasey, 1995). The foundation for this conclusion has predominantly relied upon (1) the repetitive observation of unique clinical features that cannot be attributed to other well-defined medical conditions, and (2) the amelioration of this illness in some patients following implant removal (Kaiser et al.,1990; Vasey et al., 1994;

Brautbar et al., 1995; Cuellar et al., 1995; Vasey, 1995). Supportive laboratory findings in symptomatic implant recipients have been reported (Press et al., 1992:Vojdani et al., 1992; Kossovsky et al., 1993; Campbell et al., 1994; Cuellar et al., 1994;Kossovsky and Petrovich, 1994; Kossovsky and Stassi, 1994; Kossovsky et al., 1994; Ojo-Amaize et al., 1994; Bar-Meir et al., 1995; Brautbar et al., 1995; Cuellar et al., 1995; Smalley et al., 1995; Marcus, 1996), but some of these have recently been subjected to critical review.

Historically, a useful description of a new rheumatic disorder has incorporated the simultaneous observations of both the clinical manifestations and the disease chronology. A detailed time sequence of disease development and progression often strengthens the distinction of the new entity from other classical connective tissue diseases. A prime example of this is Lyme disease, where lab tests are not always definitive, and where overlapping clinical features not infrequently create confusion and controversy due to incomplete documentation of chronological data (Steere,

1989). The present study was designed to examine the time sequence and incremental evolution of the systemic illness manifested by recipients of silicone gel-filled breast implants. The reported findings attest to the existence and uniqueness of silicone-induced disease, contribute to its definition, provide guidance and advice for the timing of explantation, and offer insight into potential mechanisms of disease causation.

MATERIALS AND METHODS

Three hundred patients (299 women and one male) who became systemically ill following insertion of silicone gel-filled breast implants were examined. The patients were either self-referred, attorney-referred, or physician-referred. Table 1 lists the indications for surgery, with two-thirds of the women having undergone bilateral cosmetic breast enhancement. Multiple different manufacturing devices were represented in the cohort as a whole. The average silicone gel device exposure spanned 12 3/4 years with implantation time ranging from 11 months to 27 years. During this interval 164 patients had only one set or a single implant inserted, and 136 patients underwent multiple

implant exchanges. A single rheumatologist interviewed and examined each patient directly, and prior medical records were reviewed whenever possible. Follow-up was arranged by either reexamination or telephone contact. In any patient with a final gel exchange for saline (44 out of 300), the additional saline device insertion time was not counted as part of

the total implant exposure time.

TABLE 1. General Features and Indications for Surgery

No. of patients	261 out of 300 bilateral
199	Cosmetic augmentation
48	Cancer (32 unilateral)
24	Post partum breast atrophy
17	Congenital/acquired (6 unilateral)
11	Fibrocystic mastitis (1 unilateral)
1	Sex change

Note: Patient population 300 (299 women). Age 16-64 (mean 33). Initial insertion from 1967-1991.

For each systemic symptom and sign recorded, the precise time of onset of each item after implantation was determined. Any single clinical manifestation was included as part of the disease process only if it was (1) chronically unremitting and/or persistently repetitive, (2) was not present prior to device insertion, and (3) could not be attributed to any other well-defined medical condition. An average of thirty symptoms and signs developed in each patient. Individual patient elapsed time analysis was performed for each increment of six symptoms and signs, and the intervals were then averaged for the group as a whole. Thus, 20% of the total disease process represented (and coincided with) the average elapsed time interval until the sixth symptom or sign was recorded. Similarly, 40% of the total disease process represented (and coincided with) the average elapsed time interval until the twelfth symptom or sign was recorded. Analyses were also performed for the eighteenth and twenty-fourth phenomena,

representing 60% and 80 % of the total disease process respectively. Data were also tabulated for presenting features, overall disease onset, and patterns of early, late, and random disease manifestations. Disease development data were not analyzed according to the type of implant inserted.

Implant rupture was determined by any of the following: obvious signs on physical examination, positive radiographic procedure, surgical findings, pathology findings, or classical history (such as sudden flattening). For patients with multiple sets of implants, rupture time was calculated only for the set that had failed, not from the total time interval since initial implantation. For example, if a patient underwent implant exchange two years from the time of initial implantation for painful capsular contracture without rupture, and the second set of implants subsequently ruptured six years later, the time to rupture was calculated at six years. If a patient experienced rupture in more than one set of implants, the incidence of rupture was counted only once, and the time to rupture was calculated for the first ruptured set only. The relationship of rupture and other local breast phenomena to the onset and progression of systemic disease was also analyzed.

RESULTS

The onset of systemic disease symptoms and signs occurred an average of 2 1/2 years after implant insertion, beginning as early as two weeks after implantation or as late as 18 years afterwards. Systemic disease development preceded implant rupture. Stated another way, implant rupture was not the stimulus for disease onset and preceded systemic illness in only nine patients (3 %). The average rate of rupture was noted to be 5% per year, and its relationship to disease onset is graphically illustrated in Figure 1.

FIGURE 1. Bar graph comparing the percentage of patients who are systemically ill vs the percentage of patients who have a ruptured implant, at two-year intervals from the time of implantation.

An average of thirty symptoms and signs developed in each patient, with the predominant clinical features listed in Table 2. Table 3 provides the average calculation of the percentage of total systemic disease that had become

established at varied points in time from implantation. These numbers are graphically illustrated in Figure 2, where the linear rate of rupture is superimposed. The disease development curve, noted in Figure 2, bears no resemblance to the usual clinical courses encountered in nonsilicone patients with classical connective tissue diseases, the latter of which is noted in Figure 3. The severity of the silicone gel related illness increased exponentially with increasing length of time of gel device insertion. Disease acceleration occurred five to six years from the time of implantation, and coincided with failure of the fibrocollagenous capsule (a local breast phenomenon clinically characterized by displacement and malposition) (Brawer, 1996). There was no difference in the rate of sequential disease development in the patients who never experienced a ruptured implant (86 out of 300) versus the patients who did experience one or more implant ruptures (214 out of 300). Rupture served to exacerbate and aggravate any systemic disease symptoms and signs that were already present, but did not change the disease development curve with regards to the production of additional new symptoms and signs. Findings also did not vary according to age at the time of implantation, the reasons for implantation, or the presence of a unilateral prosthesis. The following case history provides an example of disease

evolution.

TABLE 2. Frequency of the Most Common Symptoms and Signs, Organized According to Pattern of Onset

Clinical Features					
Early	%	Random	%	Late	%
Fatigue	(88%)	Dry eyes/mouth	(76%)	Cognitive	(64%)
Arthritis	(86%)	Morning stiffness	(69%)	Telangiectasias	(59%)
Chest pain	(77%)	Myalgias	(60%)	Freckling	(51%)
Hair loss	(59%)	Skin rash	(58%)	Pigment changes	(50%)
Headaches	(46%)	Paresthesias	(56%)	Metallic taste	(40%)
Nails	(44%)	Itching			