Articles

Antinuclear Antibodies and Breast Implants

HENRY N. CLAMAN, MD, *and* ALASTAIR D. ROBERTSON, PhD, *Denver, Colorado*

Based on a paper presented at the annual meeting of the Western Association of Physicians, Carmel, California, February 1993.

Anecdotal reports have linked silicone breast implants to autoimmune diseases, with scleroderma being mentioned most often. In view of other environmental influences—such as silica mining and the toxic oil syndrome—thought to predispose to scleroderma, more systematic immunologic information on women with silicone implants is needed to assess any possible relation to autoimmunity.

A cross-sectional survey was carried out with 150 women, of whom 131 had implants. Group 0 consisted of 19 volunteer women without breast implants who felt healthy, group I was 38 volunteer women with breast implants who felt healthy, group II was 82 women with implants who had various symptoms, and group III was 11 women with implants who had autoimmune disease. Scleroderma was overrepresented in group III (6 of 11). Antinuclear antibodies were determined on Hep-2 cells, using serum dilutions of 1:16, 1:64, and 1:256. A positive test was indicated by 1+ or more fluorescence at 1:256. Antinuclear antibody tests were positive in 0% of group 0, 18% of group I ($P < .05$ versus group 0), 26% of group II, and 64% of group III. There was no correlation between antinuclear antibody positivity and type of implant, indication for implantation, time since first implantation, total number of implants, and report of implant leak or rupture.

Women with breast implants may be at risk for the development of antinuclear antibodies. Proof of such an association will require large-scale prospective studies and epidemiologic analyses.

(Claman HN, Robertson AD: Antinuclear antibodies and breast implants. West J Med 1994; 160:225-228)

Controversy has recently arisen as to whether women with breast implants may have autoimmune abnormalities. In particular, reports of patients with breast implants who also have scleroderma[1,2] or other autoimmune syndromes[3,4] have raised the possibility of "human adjuvant disease,"[5] which would be a counterpart of the inflammatory synovitis seen in rats after the administration of complete Freund's adjuvant. Because of the scarcity of systematic studies of a reasonably large number of women, the issue of whether breast implants are associated with autoimmune changes remains in doubt.[6] In fact, a definite association between breast implants and any autoimmune manifestation remains to be established.

Patients and Methods

We measured antinuclear antibodies (ANA) in the serum of four groups of women. The protocol was approved by the Internal Review Board of the University of Colorado (Denver) School of Medicine. Informed consent was obtained after the nature of the investigation was explained. In each group, women were studied consecutively without selection. Group 0 included 19 volunteer women who did not have breast implants and who considered themselves healthy. They entered the study and received payment for a blood specimen. Group I consisted of 38 women with breast implants who felt well and who volunteered to participate as control subjects. These women learned of our study by word of mouth and from the news media (there were no advertisements). They were pleased with their implants and thought that implants should remain available. Group II consisted of 82 women with breast implants who had various symptoms including fatigue, arthralgias, and myalgias, but in whom a definite diagnosis of autoimmune connective tissue disease could not be made. (Many of these patients have some of the characteristics of fibromyalgia,[7] but this was not included as a separate autoimmune condition). These women had been referred by plastic surgeons, rheumatologists, primary care physicians, through the news media, and through a local breast implant support group. Group III comprised 11 women with breast implants who had overt connective tissue diseases—6 with scleroderma, 2 with systemic lupus erythematosus (SLE), 2 with rheumatoid arthritis, and 1 with Sjögren's syndrome. These

From the Departments of Medicine (Drs Claman and Robertson) and Microbiology/Immunology (Dr Claman), University of Colorado School of Medicine, Denver.
This study was funded in part by the National Institutes of Health General Clinical Research Center grant RR00051 and by Dow-Corning, Inc.
Reprint requests to Henry N. Claman, MD, Div of Allergy and Clinical Immunology (B164), University of Colorado School of Medicine, 4200 E Ninth Ave, Denver, CO 80262-0164.

ABBREVIATIONS USED IN TEXT

ANA = antinuclear antibody
ANOVA = analysis of variance
SLE = systemic lupus erythematosus

women were referred by the same mechanisms as were the group II women. Their diagnoses were made by rheumatologists using criteria of the American College of Rheumatology.

Each woman in groups I, II, and III filled out a detailed questionnaire and had a history and physical examination. The questionnaire included historical data, such as the date of placement of all implants (some women had as many as 8), indications for implantation, type(s) of implant, reported overt leakage or rupture, the duration of symptoms, and other medical conditions. It also provided space for the women to describe the types and severity of their symptoms (if any).

Antinuclear antibody levels were measured in an independent laboratory. The technique used Hep-2 cell substrates in a standard indirect immunofluorescence assay, and the slides were read "blindly." Serum specimens were diluted 1:16, 1:64, and 1:256. An "ANA score" was established according to the degree of positivity at 1:256.

Statistical Methods

In the primary statistical analysis, we looked at ANA levels as a function of group. In various contexts, group was considered as a nominal variable (contingency table), an ordinal variable (nonparametric analysis of variance [ANOVA]), or an interval variable (parametric ANOVA and regression). In our analysis we also considered control variables such as the indication for implantation, the total number of implants, age at implantation, and type of implant.

Results

Table 1 gives the characteristics of the four groups of women. Significant differences in age were found across the four groups (ANOVA, $P < .01$). Group 0 was younger than the other three groups pooled (linear contrast, $P < .01$). Nevertheless, when age was considered as a covariable, there were no important differences in any of the analyses. There were no significant differences among groups I, II, and III with regard to the indications for or types of implants (contingency table, ANOVA). Most of the implants (95%) contained silicone gel, and 66% were inserted for cosmetic reasons. Nearly all (99%) of the women were white.

Figure 1 shows the results of the ANA tests. A positive ANA test over all groups was not correlated with age (unpaired t test). This increase in ANA positivity from group 0 to group III is significant (contingency table, 3 degrees of freedom; $P < .01$; logistic regression, $P < .01$), but it is independent of age. The prevalence of ANAs in women with implants who felt well (group I) was significantly greater than in healthy controls without implants (group 0) (unpaired t test, $P < .05$). If group III is omitted from the analysis because of possible ascertainment bias—that is, they entered the study knowing that they had autoimmune disease—the prevalence of ANAs was still strongly related to groups 0 to II (contingency table, $P < .05$; logistic regression, $P < .05$).

For groups 0, I, and II, the patterns of positive ANA staining were almost exclusively of the fine speckled type, and the "ANA profiles," that is, anti-double-stranded DNA, anticentromere, anti-SS-A, anti-SS-B, and antiribonucleoprotein assays, were negative.

As shown in Table 2, for women with positive ANA tests, mean ANA scores were similar for groups I and II

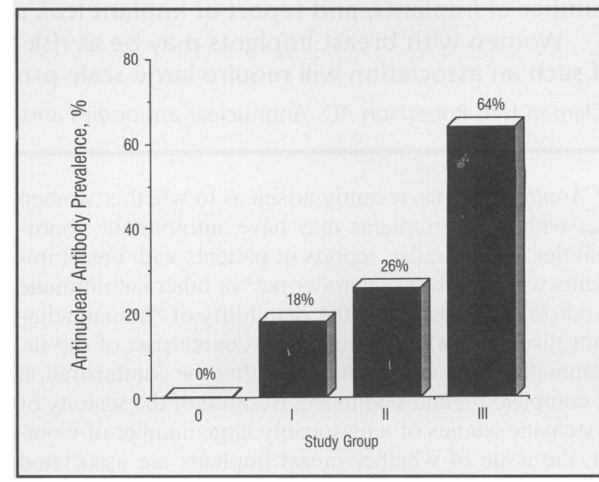

Figure 1.—The graph shows the prevalence of antinuclear antibodies at a titer of 1+ at 1:256 or stronger in four groups of women. See Table 1 for a clinical description of the four groups.

TABLE 1.—*Characteristics of 150 Women With Breast Implants*

Group	Clinical Characteristic	Subjects, No.	Age, yr ± SD	Implant Type*†			Implant Indication*		
								Reconstruction	
				Silicone	Saline	Double Lumen	Cosmetic Augmentation	Fibrocystic Disease	Cancer
0	No implants, healthy	19	38.8 ± 8.5						
I	Implants—well	38	45.2 ± 9.0	29	3	4	29	2	7
II	Implants—fatigue, musculoskeletal symptoms	82	47.2 ± 8.9	63	4	14	49	19	14
III	Implants—autoimmune disease	11	49.9 ± 10.7	10	0	1	8	2	1

*Information regarding implant type and the indication for implantation is not provided for group 0, as this is the control group.
†The type of implant is unknown for 2 women in group I and 1 woman in group II.

TABLE 2.—*Antinuclear Antibody (ANA) Scores by Group*

Group	Women, No.	Women With Positive ANA Test	Mean ANA Score* of Those With Positive ANA Test
0	19	0	NA
I	38	7	1.6
II	82	21	1.8
III	11	7	2.9

*The ANA score is determined by the degree of positivity at a dilution of 1:256:0 positivity = ANA score of 0, 1+ positivity = ANA score of 1, 2+ = 2, 3+ = 3, and 4+ = 4.

but significantly higher for group III when compared with groups I and II combined (unpaired *t* test, $P = .01$).

In group III, the ANA details were as follows: Of the six patients with scleroderma, three had the CREST syndrome (calcinosis cutis, Raynaud's phenomena, esophageal dysfunction, sclerodactyly, and telangiectasia; two were positive for ANA and anticentromere, and one was negative for ANA). Three women had diffuse scleroderma. Two had positive ANA tests (one with speckled and one with nucleolar patterns), and one did not (ANA-negative). Both patients with SLE had speckled ANAs. One had anticentromere antibodies, and the other had SS-A and SS-B antibodies. The patient with Sjögren's syndrome had ANAs, speckled pattern, and SS-A and SS-B antibodies. One patient with rheumatoid arthritis had ANAs, speckled pattern; the other patient with rheumatoid arthritis was ANA-negative. The one patient with diffuse scleroderma who was tested for Scl 70 was ANA-negative.

Possible implant rupture was assessed on the basis of history and findings at physical examination, mammography, or surgery; these data were correlated with ANA positivity. In group I, there were three ruptures (33% ANA-positive); in group II, there were 23 ruptures (22% ANA-positive). In group III, five women had ruptured implants, and all of the women were ANA-positive. Five women had no ruptures, and two were ANA-positive (40%). In one woman who was ANA-negative, the possibility of rupture could not be adequately assessed.

The period of time from first implantation to date of clinic visit (± standard deviation) was 10.0 ± 5.9 years (group I), 11.9 ± 6.1 years (group II), and 15.3 ± 4.3 years (group III). Although these do not differ significantly from each other taken in pairs, when group status (I to III) is considered as a continuum, group is correlated positively with time since first implantation ($P < .01$). Thus, women with connective tissue disease (when seen) had implants far longer than women with fatigue and musculoskeletal symptoms (group II) or women without symptoms (group I). The length of time from first implant to symptoms did not differ from group II (5.5 years) to group III (6.0 years).

There was no association between ANA positivity and type of implant, indication for implantation, or time since first implant.

When a multiple logistic regression analysis was carried out using group, age, number and duration of implants, possible leak, indication for implants, and type of implant, only group status remained significantly correlated with ANA positivity.

Discussion

In these studies we examined the relationship between breast implants and autoimmunity by measuring antinuclear antibodies in a cross-sectional analysis.

The following are the main findings:

- Significant positive ANA tests occur with a higher-than-expected frequency (18%) in women with breast implants who consider themselves healthy, when compared with controls (0% positive ANA tests);
- Many women with breast implants have a variety of complaints, including fatigue and musculoskeletal symptoms, that postdate the implants; they also have positive ANA tests (26%);
- In women with breast implants in whom connective tissue disease later developed, scleroderma was far more prevalent than rheumatoid arthritis or SLE.

We are cognizant of various types of bias that may exist in patient accrual. As both groups 0 and I felt well and had never had previous ANA testing, there was no ascertainment bias in these groups with regard to ANA positivity. The prevalence of antinuclear antibodies in healthy women without implants (group 0) was 0 in 19 (0%). The prevalence of positive ANA tests in healthy women depends on the criteria used for "positive." A recent study indicated that 5% of apparently healthy women had an ANA titer of 1:40.[8] If we used 1:64 as a criterion of positivity, 1 of 19 women in group 0 had a positive test, but at 1:256, none of the women had a positive ANA test. Thus, our results in group 0 are comparable to those of other investigators. An 18% prevalence of antinuclear antibodies in group I, a comparable group of well women with breast implants ($P < .05$ versus group 0), was unexpected. Whether autoimmune disease will develop in these women is not known. One study has shown that 12% of asymptomatic women testing positive for one or more specific antinuclear antigens, including anti-DNA, anti-SS-A, and anti-SS-B, observed for five years had signs or symptoms suggestive of autoimmunity.[9] Thus, it is possible that asymptomatic women in group I who had ANAs will in the future move into group II.

Women in group II have various symptoms including severe fatigue, musculoskeletal aches and pains, and stiffness. In no case did they meet the criteria for recognizable autoimmune syndromes. A few studies have been done of women similar to those in group II but who are not recorded as having implants. Patients with fibromyalgia (86% women) had a 9% prevalence of a positive ANA test at a titer of 1:64.[10]

Group III women with overt autoimmune disease had the highest prevalence and titer of ANA, consistent with their diagnoses. The relative preponderance of scleroderma in group III (6 of 11 patients) is in accord with the general anecdotal literature where breast implants have been associated more with scleroderma than with SLE or

rheumatoid arthritis. Although the precise prevalence of scleroderma is not known,[11] it is generally agreed to be far less common than rheumatoid arthritis. Thus, the existence in group III of six patients with scleroderma but only two with rheumatoid arthritis might be considered strong evidence pointing to an association between breast implants and scleroderma. Nevertheless, the anecdotal reports that emphasize scleroderma may also make it more likely that women with breast implants and possible or actual scleroderma will seek to enter research protocols. This point remains unresolved.

The procedure of breast implantation itself is unlikely to explain the difference in ANA prevalence between groups 0 and I. There have been no reports associating ANA positivity with surgical procedures. With regard to the tissue damage involved, women in all groups had children, and the tissue damage associated with parturition is probably greater than that associated with implant placement.

While this study was being prepared for submission, Press and co-workers reported the findings of a similar series of women.[12] Of 24 patients with implants, 11 had diagnosed connective tissue disease, 7 with scleroderma and 10 with positive ANA tests. The other 13 women had rheumatologic symptoms, including myalgia, fibromyalgia, and chronic fatigue syndrome. Of these 13, 7 (54%) had positive ANA tests. The specificity of the antinuclear antibodies did not differ from that seen in similar patients without implants. The results of our studies are thus similar to those of Press and associates.

Another recent article described the cases of women with silicone implants.[13] There are similarities and differences between this report by Bridges and associates and our study. The prevalence of ANA positivity (1:80) was 8% in 12 patients with implants without clinical symptoms, whereas in our group I, 18% had ANA positivity at 1:256. The prevalence of ANA positivity in all 156 patients with implants who were symptomatic was 22%, but it is unclear how much ascertainment bias existed in the accrual of these women. Antinuclear antibodies were found in 13 of a subgroup of 29 women with connective tissue disease (a prevalence of 45%), comparable to our group III. It is of interest that 14 of these 29 women had scleroderma-like illnesses.

These results suggest that women with breast implants may be at risk for autoimmunity. This cross-sectional study should be regarded as a hypothesis-generating probe. Larger and more carefully executed analytic studies are needed to test the hypothesis that a relationship exists between breast implants and autoimmunity.

REFERENCES

1. Spiera H: Scleroderma after silicone augmentation mammoplasty. JAMA 1988; 260:236-238

2. Varga J, Schumacher HR, Jimenez SA: Systemic sclerosis after augmentation mammoplasty with silicone implants. Ann Intern Med 1989; 111:377-383

3. Kumagai Y, Shiokawa Y, Medsger TA Jr, Rodnan GP: Clinical spectrum of connective tissue disease after cosmetic surgery: Observation on 18 patients and a review of the Japanese literature. Arthritis Rheum 1984; 27:1-12

4. van Nunen SA, Gatenby PA, Basten A, et al: Postmammoplasty connective tissue disease. Arthritis Rheum 1982; 25:694-697

5. Sergott TJ, Limoli JP, Baldwin CM Jr, et al: 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; 78:104-114

6. Shons AR, Schubert W: Silicone breast implants and immune disease. Ann Plast Surg 1992; 28:491-501

7. Wolfe F, Smythe HA, Yunus MB, et al: The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum 1990; 33:160-172

8. Xu L, Chang V, Murphy A, et al: Antinuclear antibodies in sera of patients with recurrent pregnancy wastage. Am J Obstet Gynecol 1990; 163:1493-1497

9. Yadin O, Sarov B, Naggan L, Slor H, Schoenfeld Y: Natural autoantibodies in the serum of healthy women—A five-year follow-up. Clin Exp Immunol 1989; 75:402-406

10. Dinerman H, Goldenberg DL, Felson DT: A prospective evaluation of 118 patients with the fibromyalgia syndrome: Prevalence of Raynaud's phenomenon, sicca symptoms, ANA, low complement, and Ig deposition at the dermal-epidermal junction. J Rheumatol 1986; 13:368-373

11. Steen VD, Medsger TA Jr: Epidemiology and natural history of systemic sclerosis. Rheum Dis Clin North Am 1990; 16:1-10

12. Press RI, Peebles CL, Kumagai Y, Ochs RL, Tan EM: Antinuclear autoantibodies in women with silicone breast implants. Lancet 1992; 340:1304-1307

13. Bridges AJ, Conley C, Wang G, Burnes DE, Vasey FB: A clinical and immunologic evaluation of women with silicone breast implants and symptoms of rheumatic disease. Ann Intern Med 1993; 118:929-936