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  - Polski
  - Português
  - Русский
  - Türkçe
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  - 繁體中文
  - 日本語
  - 한국어
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  - Hrvatski
  - Čeština
  - Bahasa Indonesia
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  - Română
  - Slovenski
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Antinuclear autoantibodies in women with silicone breast implants

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ANTINUCLEAR AUTOANTIBODIES IN WOMEN WITH SILICONE BREAST IMPLANTS

Contents

Section: ORIGINAL ARTICLES

Clinical syndromes resembling autoimmune diseases have been reported in women who have had breast augmentation procedures. To see whether there is a humoral immune response in these diseases that is similar to the immune response in their idiopathic counterparts, we assessed the immunological specificity of antinuclear antibodies (ANAs) and certain epidemiological features in 24 patients, all of whom (with 1 exception) had received silicone gel breast implants. ANA specificities were identified by indirect immunofluorescence, immunodiffusion, western blot analysis, and immunoprecipitation of radiolabelled intracellular proteins.

Of 11 patients who had symptoms and signs that met criteria for defined autoimmune diseases, 7 had scleroderma or subsets of this disorder and the others had systemic lupus erythematosus, rheumatoid arthritis, or overlapping autoimmune diseases. High ANA titres were present in 10 of these 11 patients and the ANA specificities were similar to those found in the idiopathic forms of the corresponding autoimmune diseases. Trauma, with resultant rupture of implants, accelerated onset of symptoms. 13 other patients had autoimmune disorders of a less clearly defined nature and low titres of ANAs whose specificities could not be identified.

ANAs are associated with the development of autoimmune complications in women with silicone breast implants. Further studies are needed to see whether this relation is one of cause and effect and whether ANAs might be early serological markers preceding development of autoimmune symptoms.

Lancet 1992; 340: 1304-07.

Introduction

There have been many reports that breast augmentation procedures have led to clinical syndromes resembling scleroderma, rheumatoid arthritis, systemic lupus erythematosus (SLE), and other rheumatic diseases.(n1-n14) Other patients have clinical syndromes that are less clearly defined, for which the term human adjuvant disease has been used.(n2)

Idiopathic systemic autoimmune diseases are characterised by a high prevalence of autoantibodies, especially antinuclear antibodies (ANAs), and these diseases can be distinguished by the various specificities of ANAs.(n15) For example, for SLE the typical ANA profile can contain any one of anti-Sin, antinuclear ribonucleoprotein (anti-nRNP) (components of the family of small nuclear ribonucleoprotein particles), and anti-DNA. By contrast, scleroderma is characterised by antibodies to Scl-70 (DNA topoisomerase D, to centromere-associated proteins such as centromere antigens A and B (CENP-A, CENP-B), or to nucleolar antigens such as RNA polymerase I. These profiles, and other distinct antinuclear antibody profiles that are highly correlated with defined autoimmune disorders, have been used as serological markers for diagnosis.

The nature of the humoral immune responses in autoimmune syndromes associated with breast augmentations has not been assessed. If this response entailed production of autoantibodies that react with antigens similar to those in idiopathic disorders, there would be support for the notion that disease syndromes associated with breast augmentation are similar to their idiopathic counterparts. However, if the autoantibody specificities are different, it would raise the question of whether these clinical features represented unusual syndromes related to an immunological reaction induced by the materials used in the prosthesis. To address these questions, we have analysed the antigenic specificities of ANAs in women with silicone breast implants.

Patients and methods

Patients

24 patients from Scripps Clinic were seen from July, 1989, to January, 1992. These patients had been referred for consultation toe the Division of Rheumatology, or were self-referred because of rheumatic complaints. Each patient was asked to complete a questionnaire, which was designed to elicit a history of Raynaud's phenomenon, arthralgias, arthritis, sicca symptoms, dysphagia, oesophageal reflux, pain, tenderness or trauma at implant sites, and skin changes consisting of thickening, oedema, atrophy, ulcerations, telangiectasias, rash, and changes in pigmentation. Nailfold capillary microscopy and physical examination were done to evaluate clinical status: signs of sclerodactyly, scleroderma, Raynaud's phenomenon, synovitis, rash, alopecia, proximal muscle weakness, pulmonary dry rales, friction rubs, axillary lymphadenopathy, and hypertension were sought.

Diagnostic criteria

Diagnosis of the individual autoimmune diseases was based on the 1980 criteria of the American College of Rheumatology (ACR)(n16) for sclerodema, the ACR classification criteria of 1982(n17) for SLE, serum anti-RNP in high titre and clinical findings as described by Kasakawa et al(n18) for mixed connective tissue disease, and the 1987 revised ACR criteria(n19) for rheumatoid arthritis. Clinical and laboratory data from these patients were used to classify them into two groups. Group I consisted of patients who satisfied established criteria for systemic rheumatic disease. Group II consisted of patients who had one or more features of systemic rheumatic disease but with insufficient criteria for definitive classification.

Detection and determination of ANA specificities

Indirect immunofluorescence was done on commercially prepared HEp-2 cell slides (Bion, Park Ridge, Illinois, USA) and on mouse kidney/stomach sections (Kallestad, Chaska, Minneapolis, USA). Other cell lines that were used included HeLa S3, HEp-2, and MOLT 4 (American Type Culture Collection, Rockville,

Maryland). All sera were assayed at a starting dilution of 1/40 in phosphate-buffered saline (PBS), pH 7.4, because it has been established in this laboratory that about 5-6% of the normal population are positive for ANAs at this dilution. When the immunofluorescence pattern was indeterminate on HEp-2 or murine tissue substrates (eg, for identification of centromere antibodies), the other cell substrates were used for more definitive identification.

Antibody specificities were determined by a combination of double immunodiffusion (Oudhterlony technique), western blots, and immunoprecipitation of(n35) S-methionine-labelled cell extracts. In immunodiffusion, standard sera containing precipitating antibodies (anti-Sin, anti-nRNP, anti-Scl-70 and anti-SS-A/Ro, SS-B/La) were used as positive reference antibodies.(n20) For western blotting, MOLT-4 whole-cell extracts were used as the antigen preparation.(n21) Human sera were used at a dilution of 1/100. In every experiment, standard sera containing antibodies that blotted Sm antigens, nRNP antigens, Scl-70 (DNA topoisomerase 1), CENP-B, and SS-A/Ro, SS-B/La were run simultaneously.(n22)

For detection of antibodies toe native DNA, Crithidia luciliae was used as a substrate.(n23) A serum was judged positive for autoantibody toe native DNA if the kinetoplast stained at a serum dilution of at least 1/10.

Autoantibodies to RNA polymerase I were identified by immunoprecipitation of (n35)S-methionine-labelled cell extracts.(24) (Scleroderma sera with autoantibody to RNA polymerase I characteristically immunoprecipitates a complex of 11-13 bands from 14 kDa to 210 kDa.(n24)) A reference serum was run simultaneously with sera from patients.

Results

There were 11 group I patients (table I) and 13 group II patients (table II). Patients in group II had been given descriptive diagnoses, such as chronic fatigue syndrome, arthralgias, or myalgias, by their attending physicians. All patients were women, of whom 22 had silicone gel implants, 1 had silicone injections (patient B), and the other I had silicone injections and gel implants (F). Only 3 patients had a previous family history of any systemic autoimmune disease (rheumatoid arthritis).

- 7 of the group I patients had scleroderma or subsets of the disease. The symptoms varied from diffuse to limited skin involvement; 1 patient had CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia) and I had overlap features of scleroderma, SLE, and mixed connective tissue disease. Of the 3 SLE patients (G-I), 2 had features of overlap disease, and of the 3 rheumatoid arthritis patients (I-K), 1 had overlap features with SLE. There was a predominance of scleroderma over other autoimmune diseases in this group of patients. Mean age at silicone implantation was 33.2 years with a mean latent period of 9.8 years from implantation to onset of clinical symptoms.
- 10 group I patients were positive for ANA, and, apart from patient J who had rheumatoid arthritis, the ANAs were of high titre (320 to 040). There were distinct and characteristic patterns of nuclear immunofluorescence, including staining of centromeres in interphase and metaphase cells, speckled staining of nucleoli, and homogeneous and speckled staining of nucleoplasm. Fig 1 shows representative patterns of nuclear and nucleolar immunofluorescence. In respect of antibodies to centromere antigens (patients C and D), CENP-A and CENP-B bands (17 and 80 kDa) were positive in western blots with these sera, corresponding in reactivity to a positive reference serum from a patient with idiopathic CREST syndrome (fig 2). This panel also shows that patient A with diffuse scleroderma had antibody to Scl-70, which reacted with an identical pattern of antigens as the reference serum and blotted the native 100 kDa DNA topoisomerase I and its degradation products including the antigenic 70 kDa (Scl-70) fragment. Patient I with SLE showed reactivity with a different 70 kDa band, which is a component of U1-nRNP and was also reactive with the BB' doublet of Sm antigen. Serum from patient B (with antibody to RNA polymerase I), which was analysed by immunoprecipitation of (n35)S-methionine-labelled cells, immunoprecipitated 11-13 protein bands that ranged from 14kDa to 210 kDa, a finding that is consistent with previous studies(n24) and our previous observations (data

not shown). Many of these sera also immunoblotted other bands, some of which could have been degradation products of higher molecular weight antigens or may, in fact, represent unique autoantibodies. Sera from patients J and K, with clinical rheumatoid arthritis and seronegative rheumatoid arthritis, respectively, were reactive with bands of unknown identity. 4 of 11 patients had rheumatoid factor.

Table II shows the findings in the group II patients. Mean age at implantation (30.8 years) and interval to onset of symptoms (8.8 years) were broadly similar to the group I patients. 7 patients were ANA positive and, apart from patient L, the ANA titres were lower than in most of the group I patients. Although many protein bands were reactive in western blots, none could be definitively identified as known intranuclear or intranucleolar autoantigens.

Of the 24 patients included in this study, 14 had a history of trauma to the breast including motor vehicle, and snow and water skiing accidents, and others had manual compression closed capsulotomy procedures to relieve contractures and adhesions (table III). Such events caused rupture of the silicone gel capsules in 6 patients. The average interval between the trauma and onset of symptoms was 2.8 years which was much shorter than the interval between the breast implant procedure itself and symptom onset (8.4 years).

Discussion

We have shown that many women with silicone breast implants have ANAs that are of the same specificities as those seen in idiopathic scleroderma, SLE, mixed connective tissue disease, and Sjogren's syndrome. Scleroderma was the commonest disorder in the breast implant patients (7/24, 29%) enrolled in our study.

About 88 cases of autoimmune-like diseases associated with breast augmentation procedures have been reported. In 27 of these cases (31%), patients had scleroderma or a scleroderma-like illness, 14 (16%) had rheumatoid arthritis, 11 (13%) had SLE, 4 (5%) had mixed connective tissue disease, and 34 (39%) had unclassified diseases. According to epidemiological studies, SLE is 3-10 times more prevalent than scleroderma, and rheumatoid arthritis is more prevalent than SLE.(n26-n28) Our finding that scleroderma is the autoimmune disorder most commonly associated with breast augmentation with silicone or paraffin does not accord therefore with the epidemiological findings. We have also analysed the distribution of new patients with rheumatoid arthritis, SLE, and scleroderma seen at the Scripps Clinic over the past 10 years. A total of 1451 new rheumatoid arthritis patients, 443 new SLE patients, and 211 new scleroderma patients were seen (distribution ratio of rheumatoid arthritis/SLE/scleroderma of 6.9/2.1/1.0). Therefore, the higher incidence of scleroderma compared with SLE and other rheumatic diseases in our breast implant patients does not seem to be due to a biased patient population. We have also analysed the sera of 23 Japanese women with rheumatic symptoms after silicone or paraffin breast augmentation procedures. The clinical features of these patients have been reported previously.(n1) Like the patients from this clinic, patients with defined autoimmune disorders had ANAs in high titre and with antigenic specificities similar to idiopathic autoimmune diseases. Scleroderma was the most common diagnosis followed by SLE, mixed connective tissue disease, and rheumatoid arthritis (data available upon request).

Of all the systemic autoimmune diseases, scleroderma has been most frequency linked to occupational hazards or external agents. Scleroderma has been reported in coal miners(n30) and gold miners(n31) exposed to silica dust, in factory workers employed in the manufacture of polyvinyl components,(n32) in cancer patients treated with bleomycin,(n33) and in the toxic oil syndrome.(n34) Our findings raise the question of whether silicone (or other materials) in implants used for breast augmentation might be another such agent. Of special interest is the observation that after trauma to the breast, the interval to onset of clinical symptoms was 2.8 years compared with an average of 8.4 years between implantation and symptom onset. Although the reasons are not clear, this observation draws attention to the possibility of acceleration of clinical symptoms after traumatic events. In some of these events, the silicone gel capsule had ruptured, which might have resulted in the release of larger amounts of silicone into the blood and

lymphatic systems.

Although some of the ANAs in our patients have immunological specificities similar to those of idiopathic autoimmune disorders, there were other putative antigens on western blots that could not be identified and may represent novel autoantibody/autoantigen systems. Our data do not allow us to distinguish between the possibility that silicone exposure hastens onset of connective tissue disease in women who might have developed disease spontaneously at a later time and the possibility that exposure to silicone induced de-novo autoimmune-type diseases. Controlled prospective studies need to be done to determine whether autoimmune diseases are more prevalent in women with breast implants, and also to assess the prevalence of scleroderma relative to other systemic rheumatic diseases. The 9-10-year interval from implant to onset of symptoms also suggests that it would be important to find out whether the development of symptoms is gradual or occurs more abruptly after a certain time, perhaps related to implant rupture or to degradation of the prosthesis. In such prospective studies, de-novo appearance of ANAs might be an early serological marker for the development of autoimmune complications.

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TABLE I--BREAST IMPLANT PATIENTS WITH DEFINED AUTOIMMUNE DISORDERS (GROUP I)

Patient (n = 11)	Diagnosis	Age at implant	Yr to symptom onset	ANA titre
A	d-Scl	46	7	640
B	1-Scl	39	20	640
C	CREST	26	14	640
D	Raynaud's	34	11	320
E	1-Scl	30	2	640
F	1-Scl	32	12	320
G	Scl/SLE/ MCTD	37	5	640
H	SLE	26	14	320
I	SLE/RA/ MCTD	32	6	640
J	RA	35	8	80
K	Seronegative RA	28	9	-

Patient (n = 11)	ANA ID/ WB kDa	RF titre
A	Scl-70	640
B	RNA Pol 1	-
C	CENP-A/B	-
D	60, 69	-
E	35, 45, 75, 100	-
F	40, 66	-
G	nRNP, Scl-70 ds DNA, 30, 54, 70	320
H	Sm, SS-A	-
I	nRNP, Sm, SS-A, ds DNA	1280
J	73, 75	640
K	35, 75, 98	-

ANA ID = antinuclear antibody identity; CREST = calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, telangiectasias;
ds = double stranded; d-Scl = diffuse scleroderma;
1-Scl = limited scleroderma;
MCTD = mixed connective tissue disease;

RA = rheumatoid arthritis, RF = rheumatoid factor;
SLE = systemic lupus erythematosus; WB = western blot. - = < 40.

TABLE II--BREAST IMPLANT PATIENTS WITH UNDEFINED AUTOIMMUNE DISORDERS (GROUP II)

Patient (n = 13)	Diagnosis	Age at implant (yr)	Yr to symptom onset	ANA titre	WB kDa
L	CFS	32	2	640	73, 75
M	Fibro	28	18	80	35, 75
N	Fibro	32	14	-	30, 55, 180
O	Fibro/sicca	27	2	-	-
P	CFS	28	1	160	66, 110
Q	Fibro	25	12	-	-
R	Myalgias	28	11	-	-
S	CFS	34	7	160	28, 75
T	Arthralgias	31	16	-	-
U	CFS	37	12	-	-
V	Myalgias	25	11	160	50, 70
W	Myalgias	45	1	80	34, 50, 70
X	Myalgias	28	7	160	50, 80

CFS = chronic fatigue syndrome, Fibro = fibromyalgia, RF tire
< 40 for all patients. - = < 40.

TABLE III--BREAST IMPLANT PATIENTS WITH HISTORY OF TRAUMA

Patient (n = 14)	Age at implant (yr)(*)	Yr to symptom onset after implant	Yr to symptom onset after trauma	Type of trauma
A	46	7	2	MVA, implant ruptured
E	30	2	1	M Cap
F	32	12	4	M Cap
I	32	6	1	MVA, implant ruptured
J	35	8	5	M Cap, implant ruptured
L	32	2	2	Water skiing accident
M	28	18	4	M Cap, implant ruptured
N	32	14	3	M Cap
O	27	2	2	M Cap
P	28	1	0.5	MVA
Q	25	12	6	Snow skiing accident
S	34	7	3	M Cap, implant ruptured
T	31	16	2	M Cap
V	25	11	4	M Cap, implant ruptured

MVA = motor vehicle accident, M Cap = manual capsulotomy.
(*) Mean = 31.2 yr.

PHOTOS (BLACK AND WHITE): Fig 1--Representative patterns of nuclear and nucleolar staining by immunofluorescence (HEp-2 cells as substrate).

(a) Centromere staining associated with punctate nuclear dots. characteristic staining associated with condensed chromosomes in a mitotic cell is present in upper right corner of this photograph (patient D, table I). (b) Characteristic nucleolar and nucleoplasmic staining associated with antibody to Scl-70 (A, table I). (c) Densely speckled Sm and nRNP staining in nucleoplasm (I, table I). (d) Staining produced by antibody to RNA polymerase I. Additional staining in nucleoplasm may be associated with another antibody specificity (B, table I).

DIAGRAM: Fig 2--Western blot analysis.

Lanes 1 and 2 = normal human sera. Lane 3 = reference antiScl-70 with arrows marking 100 kDa native topoisomerase I and the 70 kDA degradation product. Lane 4 = patient A, table I. Lane 5 = reference serum with antiCENP A and B with arrows marking 17 kDA (A) and 80 kDA (B) antigens. Lanes 6 and 7 = patients D and C, table I. Lane 8 was patient I and lane 9 reference serum for anti-Sm and anti-nRNP. Arrows mark 70 kDA U1-RNP protein and BB' doublet of Sm.

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