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Autoimmune reactions in patients with silicone breast implants

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Autoimmunreaktionen bei Frauen mit Silikon-Brustimplantation

Zusammenfassung. Seit über 30 Jahren werden Silikon-Brustimplantate in der plastischen Chirurgie eingesetzt. In mehr als 100 Fällen wurde über einen Zusammenhang zwischen Silikon-Augmentation und Autoimmunerkrankungen berichtet.

In einer retrospektiven Studie wurden 36 Frauen mit Silikon-Brustimplantaten und 36 gleichaltrige Frauen untersucht. Es wurden folgende Laborbestimmungen durchgeführt: Antinukleare Antikörper (ANA), Rheumafaktor (RF), Schilddrüsen-Autoantikörper (TMS), Angiotensin-Converting-Enzym (ACE), C-reaktives Protein (CRP) sowie andere Parameter.

12 (33%) der 36 Frauen mit Silikon-Brustimplantaten zeigten erhöhte ANA-Titer von ≥ 1 : 80, dabei fand man bei einer Frau Antikörper gegen glatte Muskulatur (ASMA) von 1 : 40. Zwei Frauen boten antizytoplasmatische Antikörper (ANCA) 1 : 320 und 1 : 40 positiv, eine war zusätzlich Rheumafaktor-positiv. Zwei weitere Frauen hatten mikrosomale Schilddrüsen-Autoantikörper. Somit waren bei insgesamt 14 (39%) der Frauen Autoantikörper nachweisbar. Klinische Symptome (muskuloskeletale) waren bei einer Frau vorhanden. In der Kontrollgruppe fanden sich erhöhte ANA-Titer bei 3 (8%) Frauen ($p < 0{,}02$) und mikrosomale Schilddrüsen-Autoantikörper bei nur 1 Frau; insgesamt waren daher Autoantikörper bei 4 (11%) Frauen der Kontrollgruppe feststellbar.

Bei 14 (39%) der Frauen mit Silikon-Brustimplantaten waren Autoimmunphänomene vorhanden. Diese waren Organunspezifisch vorwiegend in Form erhöhter ANA-Titer vom heterogenen Typ. Bei keiner der untersuchten Frauen mit Silikon-Brustimplantaten waren klinische Symptome einer Kollagen-Erkrankung nach American Rheumatism Association (ARA) Kriterien nachweisbar.

Schlüsselwörter: Silikon, Brustimplantation, Autoimmunphänomen.

Summary. Silicone breast implants have been surgical routine for over 30 years. An association between silicone augmentation and immune related diseases has been reported in approximately 100 cases. In a retrospective single center study we investigated 36 non-selected women with silicone breast implants and 36 sex- and age-matched controls. Autoimmune reactions were evaluated by measuring antinuclear antibodies (ANA), rheumatoid factor (RF) and thyroid gland antibodies (TMS), along with angiotensin-converting enzyme (ACE), C-reactive protein (CRP) and other immunological and laboratory parameters. In the controls only 3 (8%) women had an elevated ANA titer and 1 demonstrated thyroid autoantibodies (microsomal), giving a total of 4 (11%) women with detectable autoantibodies. By contrast, 12 (33%) of the 36 women with silicone augmentation had raised ANA titers (≥ 1 : 80), a significantly higher percentage than in the control group ($p < 0.02$). Of the 12 women, 1 showed antismooth muscle antibodies (ASMA; titer 1 : 40) and 2 of the patients displayed antineutrophilic cytoplasm antibodies (ANCA; 1 : 320 and 1 : 40, respectively), one of the latter also being positive for rheumatoid factor. 2 further women demonstrated thyroid autoantibodies (microsomal), giving a total of 14 (39%) women in whom significant autoantibodies were detectable. Clinical symptoms (musculoskeletal) were present in 1 patient. Most of the observed autoantibodies were organ-unspecific, with a predominance of elevated ANA titers of the heterogeneous type and not related to a distinct clinical entity. However, none of the investigated women with silicone breast implants showed clinical symptoms or signs of connective tissue disease according to ARA criteria.

Key words: Silicone, breast implants, autoimmune phenomenon.

Abbreviations: ANA antinuclear antibody; sp speckled; hom homogeneous; nu nucleolar; RF rheumatoid factor; ACE angiotensin converting enzyme; CRP C-reactive protein; ASMA anti smooth muscle antibody; ANCA antineutrophilic cytoplasm antibody; IgG, IgA, IgM, IgE immunoglobins; C3c complement component 3; C4 complement component 4; IL-6 interleukin 6; TNF-a tumor necrosis factor-a; TNT-r tumor necrosis factor receptor; ARA American Rheumatism Association criteria; PVP polyvinylpyrrolidone; DID double immune diffusion; AMA antimitochondrial antibody; HTG human thyroglobulin autoantibody; TMS thyroid microsomal autoantibody.

Introduction

Over the past two decades more than one million have received silicone gel-filled implants for breast reconstruction following mastectomy or breast augmentation for various reasons. The well-documented side effects of silicone gel-filled implants are local complications associated with rupture or leakage, resulting in the release of silicone gel, and leading to the formation of foreign body granulomas and fibrous changes [1–5]. Granulomas (siliconomas) are frequently associated with local pain and discomfort. In women with silicone-breast augmentation general symptoms such as myalgia and arthralgia have also been reported [6–9]. These general symp-

toms may occur both in patients with a ruptured, and those with an intact capsula. In fact, silicone has even been identified by light microscopy in the surgically removed fibrous capsulas of patients with an intact gel-filled prosthesis [8]. Moreover, in rare cases, muscle pain and arthralgia have been observed in women in whom only saline-filled implants had been used [9]. It was also suspected that silicone gel-filled breast implants might increase the incidence of breast cancer. As a result, in the spring of 1992, the Food and Drug Administration recommended the restricted use of silicone gel-filled breast implants under carefully controlled clinical protocols. On the other hand in a recent study from Alberta, Canada, on women who had undergone breast augmentation with silicone implants, a lower incidence of breast cancer was found than in the general population [10].

Furthermore, autoimmune phenomena and immune-related connective tissue disorders have been reported in women after breast augmentation with silicone [6, 9, 11, 12]. The connective tissue disorders associated with silicone augmentation include scleroderma, mixed connective tissue disease, lupus erythematodes, rheumatoid arthritis, polyarthralgia and polymyalgia [6–9, 11–18]. In the present single center study we analysed the occurrence of autoimmune phenomena in some of our patients after implantation of silicone breast prostheses.

Patients

Thirty-six women with silicone breast implants were included in this study, all of them from the 1st Department of Plastic Surgery, University of Vienna. Specific information on the occurrence of myalgia and arthralgia or connective tissue diseases was obtained from all patients. None of the women studied had a family history of autoimmune disorders or autoimmune-related diseases, and none had any symptoms or signs of respiratory, gastrointestinal, or urogenital tract infection. In 29 women silicone breast implantation was undertaken following mastectomy for cancer, in 7 for cosmetic reasons. The mean age of the women was 52 ± 10 (range 35–81) years. The mean observation time after silicone breast implantation was 8.4 ± 6.5 (range 1–23) years; in 24 of the 36 women the observation time was 5 or more years, in 12 less than 5 years. Twenty-three women received 1, five women 2, five women 3, two women 4 and one woman 7 silicone protheses. The sex- and age-matched control subjects from the Department of Plastic Surgery Vienna were hospitalised for the following reasons: mastectomy for cancer (2), fibroadenoma of the breast (2), basalioma (2), melanoma (2) and another tumor of the skin (1), carpal tunnel syndrome (6), necrotic and/or inflammatory skin changes (6), cicatricectomy and other plastic skin corrections in healthy women (15). In the controls none of the women had received silicone implants in the past or had a family history of autoimmune disorders.

Methods

Blood was drawn from each woman after overnight fasting; it was centrifuged and the serum stored at –20 °C until analysed. Autoimmune phenomena were evaluated by the following procedures. Antinuclear antibody (= ANA) reactivity was measured by indirect immunofluorescence using rat liver cells (Bios, Germany), titers of ≥ 1 : 80 being considered positive, and confirmed using HEP-2 cells (Immunoconcepts, CA).

ANA-positive sera were further investigated by double immunediffusion (DID), ELISA and immunoblotting [19].

DID

Twenty µl of a bovine cellular extract (Immunoconcepts, Sacramento, CA, USA) was applied to the central hole of an Ouchterlony microplate (Bios, München, Germany) and allowed to react with undiluted serum from patients for 48 - hours at room temperature. Reference sera specific for the antigens Ro/SS-A, La/SS-B, Sm, U1-RNP, Scl-70 and Jo-1 served as controls; these sera had been validated previously against reference sera from the Center of Disease Control, Atlanta, GA, U.S.A.

ELISA

ELISA kits for the determination of antibodies to Ro/SS-A, La/SS-B, Sm, U1-RNP were a generous gift from Jeanne Feather, Advanced Biological Products, Ontario, Canada. The kits were used according to the instructions provided by the manufacturer. Briefly, sera were incubated at 1 : 100 dilution for 30 min with the immobilized antigens. After washing 4 × 2 min bound antibodies were detected using a horseradish peroxidase conjugated goat anti-human IgG antibody. In addition to the control sera contained in the kits our own reference sera were used as controls. The cut-off value was defined as the mean absorption + 3 standard deviations of ANA-negative control sera (usually 0.4–0.5 OD).

Immunoblotting

Nuclear and cytoplasmic extracts prepared from HeLa cells were used as antigenic sources, HeLa S3 cells were obtained frozen from the Computer Cell Culture Center, University of Mons, Belgium. Five × 10^9 cells were suspended in 20 ml of 20 mM Hepes-KOH, pH 7.4, 140 mM KCl, 1 mM $MgCl_2$, 0.5 mM DTE, and lysed mechanically by dounce homogenization. Nuclei were separated by centrifuging for 3 min at 2,000 g, and extracted as described below. The cytoplasmic supernatant was first centrifuged for 20 min at 20,000 g, and finally for 1 hour at 100,000 g, The resultant cytoplasmic S-100 extract was separated on 10% SDS polyacrylamide minigels (5 × 8 cm) and subsequently transferred to nitrocellulose membranes, which were then stored at 4 °C.

For the preparation of nuclear extracts, 5 × 10^9 nuclei were incubated for 30 min in 4 ml hypotonic buffer (10 mM Hepes-KOH, 2.5 mM $MgCl_2$, 25% glycerol, pH 7.9) and subsequently extracted for 40 min by addition of an equal volume of the same buffer containing 0.88 M NH_4Cl. The resultant slurry was centrifuged for 20 min at 20,000 g, and the NH_4Cl concentration of the supernatant was adjusted to 0.3 M by diluting with 10 mM Hepes-KOH, pH 7.9. The extract was electrophoresed on 12% SDS polyacrylamide gels (10 × 20 cm) and subsequently transferred to nitrocellulose membranes.

For immunodetection of autoantibodies, the nitrocellulose membranes were cut into strips, blocked for 1 hour in PBS (10 mM sodium phosphate, 140 mM NaCl, pH 7.2), 3% nonfat dried milk (blocking buffer), and then incubated for 40 min with patients' sera diluted 1 : 25 in blocking buffer. After washing, bound autoantibodies were detected using alkaline phosphatase coupled anti-human IgG (goat) (Accurate Chemical and Scientific Corp., Westbury, NY). Sera with strong autoreactivities to Sm, U1-RNP, Ro, La, hnRNP-A2 (RA33), Scl-70, Jo-1 and ribosomal RNP were used as references.

Analyses for other autoantibodies (antimitochondrial antibodies = AMA; anti smooth muscle antibodies = ASMA; antineutrophilic cytoplasma antibodies = ANCA) were performed by indirect immunofluorescence staining using standard commercial kits (Bios, Germany). Thyroid microsomal autoantibody (TMS) and human thyroglobulin (HTG) autoantibody were measured by immunoradioassay (Serono Diagnostics,

Germany), rheumatoid factor, serum concentrations of C-reactive protein, IgG, IgA, IgM, C3c and C4 by nephelometry (Behring). Angiotensin-converting enzyme (ACE) was measured by colorimetric assay (Bühlmann Laboratories AG, Basel, Switzerland) and neopterin by radioimmunoassay (Henning, Germany).

Patients with ANA titers ≥ 1 : 80 were re-examined 6 weeks later and DNA, ENA, AMA, ASMA and ANCA, serum levels of circulating immune complexes IgG and IgM, total IgE, IgG, IgA, IgM, C3c, C4, liver and kidney function tests were additionally determined. Circulating immune complexes were quantified and characterized using Merrid CIC kits (Mercia Diagnostics, U.K.). In addition, cytokines (IL-6 = interleukin 6, Innogenetics, Belgium; TNF-alpha = tumor necrosis factor alpha, Innogenetics, Belgium; TNF-R = tumor necrosis factor-receptor, Bender, Austria) were measured using ELISA techniques. Normal values for thyroid autoantibodies are anti-HTG 0–100 U/ml, anti-TMS 0–50 U/ml, for ACE 18–55 U/min, neopterin 0–10 nmol/l, CIC IgG 10–110 ng/ml, CIC IgM 15–115 ng/ml, CRP < 5 mg/l, IL-6 < 10 pg/ml, TNF-alpha < 10 pg/ml, TNF-R 1.47–4.16 ng/ml. The chi^2-test was used for statistical analysis.

Results

Of the 36 women with breast implants 13 patients (36%) had been checked regularly for over 10 years, 11 patients (31%) for periods between 5 and 10 years, and 12 (33%) for up to 5 years.

Indication for implantation of breast prostheses

In 29 (80%) women breast reconstruction had been carried out following mastectomy due to cancer, while 7 (20%) had undergone breast augmentation for various other reasons. Of the total of 63 silicone prostheses, 49 were filled with silicone gel, 7 with physiological saline and 7 with polyvinylpyrrolidone (PVP). Twenty-three (64%) patients received one prosthesis only, 12 patients (33%) between 2 and 4, and 1 patient had 7 prostheses implanted over the years.

Local changes

Examination of breast implants by sonography and/or mammography demonstrated capsular shrinkage, calcification and granulomas in 8 patients (22%).

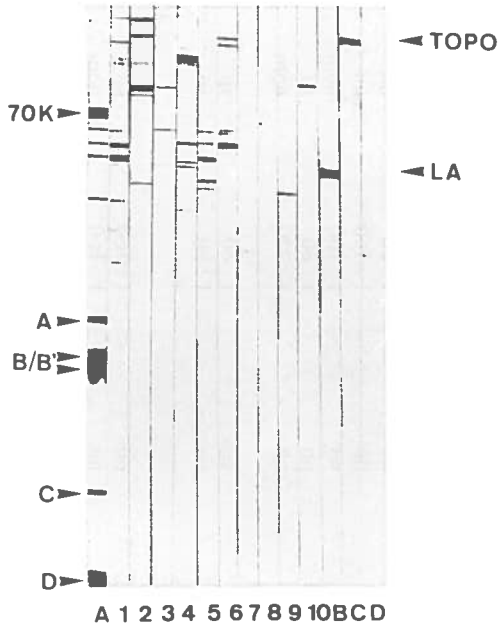

Fig. 1. Detection of antinuclear antibodies in sera by immunoblot analysis using a nuclear extract from HeLa cells as antigenic source. Ten patients' sera (lanes *1–10*) and four control sera (lanes *A, B, C, D*) were run in parallel. The positions of the antigens are indicated by arrows. *A* Anti-Sm/U1-RNP reference serum recognizing the Sm specific antigens B/B′, D and the U1-RNP specific antigens 70K, A, C. *B* Anti-La reference serum detecting the 48 kD La band. *C* Anti-Scl-70 (topoisomerase) reference serum detecting the 100 kD band of topoisomerase (topo). *D* Negative control serum

Laboratory screening test

Elevated ANA titers of ≥ 1 : 80 were found in 12 (33%) patients, one of these having a positive rheumatoid factor. Thyroid microsomal antibodies were present in 2 (6%) patients. Thus, autoimmune phenomena were detected in 14 (39%) of the 36 women studied. Increased ACE levels were found in 12 (33%) out of 36 patients, whereas CRP was only slightly increased in 3 (8%) patients. None of the patients showed an elevated neopte-

Table 1. *Immunological and laboratory parameters in women with silicone augmentation (n = 36) and sex- and age-matched controls (n = 36)*

Test	Patients number	(%)	Controls number	%	
ANA (total)	12	(33)	3	(8)	p < 0.02
1 : 80	6	(17)	1	(3)	
1 : 160	4	(11)	2	(5)	
1 : 320	2	(5)	0		
RF	1	(3)	0		
HTG	0		0		
TMS	2	(5)	1	(3)	
ACE	12	(33)	12	(33)	
CRP	3	(8)	8	(22)	
Neopterin	0		0		

ANA Antinuclear antibody, *RF* rheumatoid factor, *HTG* human thyroglobulin autoantibody, *TMS* thyroid microsomal autoantibody, *ACE* angiotensin converting enzyme (normal up to 55 U/l), *CRP* C-reactive protein (normal up to 5 mg/l). Assays (by indirect immune fluorescence, colorimetry or radio ligand binding) were performed using standard commercially available kits

Table 2. *Clinical data of the patients with elevated ANA titer*

	Patient	Age	Primary diagnosis	Prosthesis	Follow-up (yr)	Local changes	Musculoskeletal pain	ANA titer	ANA type
1	G. E.	55	Ca	silicone	11	no	no	1 : 80	sp
2	P. A.	52	mastopathy	silicone	10	granuloma	no	1 : 320	sp
3	D. M.	39	Ca	silicone	8	no	no	1 : 80	nu
4	H. M.	42	Ca	saline-silicone	3	no	no	1 : 160	nu
5	M. A.	42	mastopathy	silicone	2	no	no	1 : 160	hom
6	W. B.	51	Ca	PVP-silicone	1	no	no	1 : 80	sp
7	G. M.	76	mastopathy	silicone	19	calcifications granuloma	no	1 : 320	hom
8	J. G.	51	Ca	silicone	8	calcifications	yes	1 : 80	sp
9	S. R.	47	mastopathy	saline-silicone 1970 silicone 1988 PVP 1991	22	no	no	1 : 80	sp
10	S. E.	49	Ca	silicone	5	calcifications	no	1 : 160	sp
11	V. M.	46	Ca	saline-silicone	4	no	no	1 : 160	hom
12	K. G.	69	Ca	silicone	2	ca relapse	no	1 : 80	sp

sp Speckled, *hom* homogeneous, *nu* nuceolar. Age, primary diagnosis, kind of augmented prosthesis, follow-up, local changes and muskuloskeletal pain in the 12 women with elevated antinuclear antibodies (*ANA*)

Table 3. *Circulating immune complexes, IgG, IgA, IgM, C3c and C4 levels in the women with elevated ANA titer*

	Patient	Circulating immune complexes								
		IgG ng/ml	IgM ng/ml	IgE (total) U/ml	IgG mg/dl	IgA mg/dl	IgM mg/dl	C3c mg/dl	C4 mg/dl	ANA titer
1	G. E.	55	85	30.5	1280	184	284	94	26	1 : 80
2	P. A.	62	59	5.0	1470	370	486	80	33	1 : 320
3	D. M.	11	22	16.1	1270	194	281	81	28	1 : 80
4	H. M.	18	< 3	44.7	1810	178	194	77	36	1 : 160
5	M. A.	32	16	49.4	1660	290	289	92	31	1 : 160
6	W. B.	11	25	15.3	904	204	174	57	25	1 : 80
7	G. M.	39	19	21.2	725	125	173	81	40	1 : 320
8	J. G.	11	< 3	214.9	1190	239	125	101	23	1 : 80
9	S. R.	4	< 3	5.0	1210	135	245	83	29	1 : 80
10	S. E.	31	55	nt	1920	326	269	101	29	1 : 160
11	V. M.	71	11	nt	1300	241	135	72	24	1 : 160
12	K. G.	nt	nt	nt	nt	nt	nt	nt	nt	1 : 80

Circulating immune complexes, immunoglobins IgE, IgG, IgA, IgM, complement components C3c and C4 levels in the silicone augmented women with elevated antinuclear antibodies (*ANA*).

Table 4. *Interleukin-6, tumor necrosing factor and receptor, CRP and ACE levels in patients with elevated ANA titer*

	Patient	IL-6 < 10 pg/ml	TNF-α < 10 pg/ml	TNF-r 1.47–4.16 ng/ml	CRP 5 mg/ml	ACE 18–55 U/min	ANA titer
1	G. E.	< 3.0	29.0	0.8	< 5	77	1 : 80
2	P. A.	3.5	4.4	1.1	10	32	1 : 320
3	D. M.	20.5	7.7	1.1	< 5	56	1 : 80
4	H. M.	7.7	12.0	1.3	< 5	60	1 : 160
5	M. A.	3.0	13.5	1.3	< 5	56	1 : 160
6	W. B.	< 3.0	6.4	1.3	< 5	51	1 : 80
7	G. M.	4.8	10.0	2.0	< 5	55	1 : 320
8	J. G.	< 3.0	5.6	1.5	< 5	55	1 : 80
9	S. R.	10.9	13.0	1.4	< 5	44	1 : 80
10	S. E.	nt	nt	nt	< 5	51	1 : 160
11	V. M.	nt	nt	nt	7	69	1 : 160
12	K. G.	nt	nt	nt	< 5	43	1 : 80

Interleukin-6, tumor necrosis factor and receptor (*TNF*), c-reactive protein (*CRP*) and angiotensin converting enzyme (*ACE*) in the silicone augmented women with elevated antinuclear antibodies (*ANA*).

rin level. In the sex- and age-matched controls elevated ANA titers (≥ 1 : 80) were found in 3, thyroid microsomal antibody in 1, CRP (> 5 mg/l) in 8 and ACE (> 55 U/l) in 12 women. Both RF and neopterin were within reference levels. Consequently, the prevalence of an elevated ANA titer was significantly higher in the women with silicone breast implants than in the controls (12/36 vs 3/36, $p < 0.020$, chi^2 test) (Table 1).

Detailed analyses

The individual data of the patients with elevated ANA titers ≥ 1 : 80 who participated in the detailed analyses are listed in Table 2. The primary diagnosis was breast cancer in 8 patients, mastopathy in 4 patients. Four of these patients had been followed up for over 10 years. Local changes were present in 4 patients and musculoskeletal pain only in 1. Detailed analyses confirmed the elevated ANA titers in the 12 patients; ds-DNA autoantibodies were not detectable in any of these patients. ANA typing of HEP-2 cells showed that the speckled type was predominant, followed by the homogeneous and nucleolar types. Only 1 serum (P.A.) showed a precipitation line in DID, all other sera were not reactive in this assay. The reactivity in serum P.A. could not be identified since there was no identity with any of the reference sera employed. Similarly, none of the sera was clearly positive in ELISA. In contrast, immunoblotting revealed reactivities directed to nuclear antigens, particularly in sera 1–6 (Fig. 1). Interestingly, no reactivities to cytoplasmic antigens were detectable (data not shown). The nuclear autoantigens recognized by these sera could not be identified since they were clearly different from well defined specificities such as SM, U1RNP, or Scl-70. Nevertheless, 2 sera (1 and 5) apparently stained the same 50 kd band, and sera 4 and 6 were reactive with an antigen of approximately 60 kd. Possible identities were also observed between sera 2 and 3 (80 kd). Most reactivities were directed to proteins of relative high molecular weight (> 50 kd).

ASMA was detectable in one patient (V. M.), ANCA in two patients (G.M.), (V.M.) and RF was positive in one patient (G.M.). Of the remaining immunological parameters studied, circulating immune complexes IgG and IgM serum concentrations of IgG, IgA, C3c and C4 were negligible. The total IgE was markedly increased in 1 patient (G.J.), the IgM moderately elevated in 1 (Table 3). There was no evidence for consumption of complement fractions C3c or C4. Interleukin-6, TNF-alpha and CPR showed individual variation; there were no significant differences between the women with silicone breast implants and the controls. Five of the 12 patients with elevated ANA titers showed increased ACE levels (Table 4).

Discussion

Silicone breast implants are widely used in reconstructive and aesthetic surgery. Mechanical compression can produce leakage or rupture of the capsula, with loss of silicone and consequent shrinkage of the implant. Fibrous and granulomatous changes, as well as calcification are detectable sequelae [1–5]. Activated fibroblasts, fibronectin and other proteins and macrophages with phagocytic activity were found in biopsies obtained from capsulotomy and capsulectomy specimens [1–5]. Silicone particles were present in the cytoplasm of these macrophages [1]. It is possible that the total amount of tissue silicone and the

number of macrophages loaded with phagocytosed material can be correlated with the intensity of the reaction [1, 4]. However, there is every reason to believe that in most cases the macrophage activity is a chronic reaction restricted to the silicone capsula or silicone particles. In our study we found no intensive macrophage activity, the serum level of neopterin – a pteridine released from stimulated macrophages – not being elevated in any patient. The "acute phase proteins" (e.g., interleukin-6) were seldom elevated, and if so only slightly and showing an individual pattern. The absence of generalized inflammatory reactions can be inferred from these findings. In some case reports [6–9, 11–18] an association between silicone augmentation and the development of autoimmune disorders has been postulated, whereby the clinical spectrum of silicone-induced autoimmune diseases included lupus erythematodes, rheumatoid polyarthritis, progressive systemic scleroderma and Hashimoto's thyroiditis [11–18]. Weismann et al. [20] and Fisher [21] concluded that there is no convincing evidence that silicone implants cause any generalized disease. In our single center study autoimmune phenomena were found in 14 of 36 patients (39%). Antinuclear antibodies present in 12 (33%) patients were the most common type of immunological reaction. These were heterogeneous, with predomination of the speckled type, followed by homogeneous and nucleolar types (Table 2). Immunoblotting confirmed the presence of nuclear antigens (Fig. 1). Interestingly, in at least some cases identical precipitation lines were observed. The classical marker of lupus erythematodes, anti-ds DNA was not detectable in any of the patients. Although LE specific markers were not present, elevated ANA levels and the occurrence of autoantibodies detected by immunoblotting suggest considerable autoimmune reactions in these patients. Antineutrophilic cytoplasm antibodies were present in 2 patients and rheumatoid factor in 1 of these, whilst antismooth muscle antibodies were detected in a third patient. Nevertheless, it is noteworthy that only one patient out of the 12 ANA-positive patients had musculoskeletal pain, without any symptoms or signs of connective tissue disease. The proportion of patients with breast cancer developing autoimmune phenomena was 8 of the 29 (28%) who received silicone implants. Therefore, the possibility that breast cancer plays a role in the development of immunological phenomena cannot be excluded. However, the only association between breast cancer and autoimmunity reported so far is paraneoplastic cerebellar degeneration [22] and hypothyroidism [23]. Furthermore, in our study 4 of the 7 patients without breast cancer developed autoimmune reactions after silicone augmentation.

In the controls autoimmune phenomena were found in 4 of 36 women (11%); of these, 3 had an elevated ANA titer and 1 had microsomal thyroid antibodies. None of the 4 control women with breast cancer or fibroadenoma developed autoimmune phenomena; of the 9 women with various tumors of the skin only 1 woman with melanoma developed an autoimmune reaction. Hence, a direct association between breast cancer and the development of autoimmune reactions seems unlikely.

Kumagai et al. [17] reported on 18 patients who had undergone cosmetic surgery and found increased ANA titers of speckled or homogeneous types in 3 patients, rheumatoid factor in 5, and Hashimoto's thyroiditis in 2 patients. Organ specific (microsomal) antibodies to the thyroid gland are rare in silicone augmented women; only 2 of the 36 patients in our study demonstrated these antibodies, without any accompanying clinical manifestations. Similar observations have been reported by Endo et al. [18]. Removal of the implants may be associated with improvement or even disappearance of the signs and symptoms, but is indicated only when the symptoms cannot be managed with non-steroid drugs. Kaiser et al. [12] and Heredero [9] observed an improvement of clinical symptoms after removal of silicone implants, and a decrease or even normalisation of the markedly raised ANA titers and other immunological parameters, including ACE. The question arises, however, as to what length of follow-up is necessary for the detection of the development of autoimmune reactions in silicone-augmented patients. The average length of follow-up in our study was 8.4 years. Of the 14 patients in whom autoantibodies were present, 6 had been followed up for 10 or more years, the others for periods between 1 and 8 years.

It is not known why only some patients develop autoimmune reactions to silicone. The detection of antibodies to silicone elastomers in 2 patients with ventriculoperitoneal shunts seems to be the way to clarify the silicone-induced immunological reaction [24]. Estimation of ACE in the blood is not an adequate screening test for silicone micro- and macrogranuloma formation around the prosthesis. In both patients and controls the number of subjects with elevated ACE levels was identical (12 of 36). A decrease in the previously elevated ACE level was observed in 1 case after removal of the silicone prostesis [12]. Our study demonstrated that there is an increased incidence of autoimmune reactions, predominantly raised ANA titers, in patients with silicone breast implants. These reactions are generally organ unspecific and heterogeneous, as reported also by others [25]. Bridges et al. [26] found antinuclear antibodies in 22%, and rheumatoid facttor in 9% of 156 silicone patients referred to them for symptoms of rheumatic disease. Gabriel et al. [27] found no association between silicone breast implants and connective tissue disease in their study. By contrast, Teuber et al. [28] found antibodies to collagen in 35% of the women with silicone breast implants. Salomon et al. [29] and many others believe that many symptomatic women with silicone breast implants have a new rheumatic syndrome characterized by myalgia, polyarthralgia, chronic fatique and neurologic disturbances. In our small group of women with silicone breast augmentation an elevated ANA titer was found in a third of the patients; however, none of the women developed symptoms or signs of connective tissue disease.

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