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Silicone granulomatous lymphadenopathy and siliconomas of the breast

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Summary. In the present study, two histologically-distinct cases of granulomatous lymphadenitis induced by dimethylpolysiloxane (silicone polymer) implants were studied. Four and six years after implant, and following surgery for breast cancer, painful homolateral axillary adenopathies were observed and biopsied. In both cases, histological examination led to a diagnosis of "silicone-induced granulomatous adenitis" requiring removal of implants. Foreign-body granulomas (siliconomas) were observed in surrounding tissue with no apparent rupture of implant capsules; however, visible retraction, hardening and scattered calcifications were noted. The presence of silica was revealed by incineration of a number of biopsied lymph nodes, a technique not hitherto used in the study of this pathology. A review is offered of the literature available.

Key words: Silicone, Siliconoma, Granulomatous lymphadenitis, Mammoplasty, Silica

Introduction

Over the last 30 years (Duffy and Woods, 1994; Friedman, 1994), almost 2 million American women have received silicone implants (Emery et al., 1994), the most common types being the implant developed by Ben-Hur et al. (1967) and subsequent modifications by Rudolph et al. (1978) and Truong et al. (1988). Although implant material was initially defined as "non biodegradable" (Demergian, 1963) and harmless, its use has become the subject of considerable and ongoing controversy. Brautbar et al. (1995) have demonstrated "in vitro" that silicone is both degradable and immunogenic; silicone leaks from the implant were reported to migrate throughout the lymph and reticuloendothelial systems, (Kikuchi's syndrome, Sever et al., 1996), leading to possible autoimmunization and immune system disorders reversible in 50% to 70% of cases following implant removal. Immunogenic capacity was refuted by Smith (1995) in comparisons with standard antigens. Naim et al. (1995), while accepting in principle the "stability" of silicone, concluded that silicone constituted a powerful humoral adjuvant potentially stimulating the formation of autoantibodies to thyroglobulin and collagen. Nevertheless, the immune response produced neither thyroiditis nor arthritis.

Numerous studies report wide-ranging local (breast) and remote clinical symptoms in patients with silicone implants (Arion, 1995; Logothetis, 1995; Vasey, 1995b). These symptoms become less marked or completely disappear following implant removal. A growing number of women are dissatisfied with their breast implants and an International Association has already been set up for those women suffering from implant-related disorders and several questions have been discussed already in the Tribunals (Marshall, 1996). The most frequently reported symptoms are: frequent fatigue, (82%); joint and muscle pain (62%); neuritis, lymphadenitis, rheumatism (Vasey et al., 1995a); cutaneous lesions, chest or axillary pain (Sichere et al., 1995); dyspnoea (Celli et al., 1978); and endocarditis (Travis et al., 1986). Many of these symptoms are accompanied by impairment of the immune system (Espinoza, 1995; Schiller et al., 1995), connective tissue disorders (Valesini et al., 1995; Hochberg et al., 1996; Hochberg and Perlmutter, 1996) and modified biochemical parameter (Field and Bridges, 1996). The most frequent local symptoms are: capsular hardening and contraction (Friedman, 1994; Thuesen et al., 1995); and pericapsular granulomatous reactions (Sanger et al., 1995). Rosenberg (1996) studied 131 women diagnosed as having a neurological problem related to silicone breast implants. Most patients (66%) had normal neurological examinations. No pattern of laboratoy abnormalities was seen. Their conclusion: "is no evidence that silicone breast implants are causally related to the development of any neurological disease". Contrarily, Shoaib and Patten (1996) described a new syndrome that appears as a systemic inflammatory autoinmune disease within the central nervous system (multiple sclerosis-like syndrome), in twenty-six women. The median latency period betwen breast implants of

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silicone and onset of symptoms was 5.71 years.

There is much debate concerning the precise pathogenic mechanisms involved and the actual existence of a causal relationship between clinical symptoms and the presence of silicone in surrounding tissue. In order to put this problem into context, the following points should be considered:

1) Silicone diffusion

For years, scientists have warned of the possible "leakage" of silicone into tissue surrounding silicone implants (O'Hanlon et al., 1996), and even to more remote sites: (Symmers, 1968; Capozzi et al., 1978; Wintsch et al., 1978; Hausner et al., 1978; Mason and Apisarnthanarax, 1981; Rich et al., 1982; Argenta et al., 1983; Frey et al., 1992; Jansen et al., 1993; DeCamara et al., 1993; Laxenaire et al., 1994; Duffy and Woods, 1994; Brautbar et al., 1995; Freundlich et al., 1996; Shanklin et al., 1996). The possibility of injury-induced (Malata et al., 1994) or iatrogenic (DeCamara et al., 1993; Teuber et al., 1995) ruptures should not be ruled out. Teuber et al. (1995) reported deterioration of all silicone capsules 10 or more years after implant.

Several authors have discussed possible silicone migration: Greene et al. (1995) used microanalysis to identify silicone in histiocytes and extracapsular connective tissue in 12 women with implants. Silica was discovered in synovial fluid in four women (a condition also reported by Vasey et al., 1995a), and also in the skin of one woman (scleroderma). Teuber et al. (1995), using X-ray and MRI techniques, discovered traces of silicone-type material in surrounding soft tissue, and warned of its destructive effect on tissue, especially in the case of ruptured implants. Emery et al. (1994), in an electron-microscopic and infra-red spectroscopic study of 103 ruptured and 80 healthy capsules, observed giant foreign-body multinuclear cell inflammatory reactions in all cases, with no basement membrane interposition between cellular elements and implant capsules. These results led Grant and Edelman (1994) to warn against breastfeeding for women with implants. The letter of Eptstein (1996) serves in order to confirm this idea. Gedalia et al. (1995) also reported rashes and lupus in the newly born child of a mother with a silicone implant.

Malata et al. (1994) studied 51 patients presenting retraction of implant capsules. In 23% of cases, small ruptures were reported unaccompanied by either systematic complications or increased blood silica levels in tests made over 12 years after implant. Possible silicone migration has also been linked to breast cancer (Morgernstern et al., 1985; Daher et al., 1994), and lymphomas (Digby, 1982, Benjamin et al., 1982; Cook et al., 1995, Duvic et al., 1995). No increase in the incidence of sarcomas was reported (Engel et al., 1995). Potter and Morrison (1996) induced plasmacytomas in 60-70% of highly susceptible congenic mice injected with silicone gels. Garland et al. (1996) published one case of multiple myeloma in women with silicone breast implants. There has been greater controversy as regards effects on the immune system (Vojdani et al., 1992; Koeger et al., 1993, 1994; Campbell et al., 1994; Edelman et al., 1994a,b; Cohen, 1995; Cuellar et al., 1995; Mena et al., 1995; Peters, 1995; Teuber et al., 1995), the appearance of local inflammatory reactions (Karlsson et al., 1992), or inflammation of connective tissue in general (Cuellar and Espinoza, 1994; Rowley et al., 1994; Martin, 1995; Sanchez-Guerrero et al., 1995).

Doi and Refojo (1995) found small droplets ingested by mononuclear cells in the vitreus cavity or preretina at 4.6 months in silicone-fluorosilicone copolymer oil injected in rabbit phakic eyes. Knorr et al. (1996) did histological examinations on 36 enucleated globes after silicone oil injection. They observed histological changes in all layers of the eyes and vacuoles both free and incorporated by macrophages in all layers of the retina, optic nerve, choroid, ciliary body, iris, chamber angel and corneal.

Biological causes should not be ruled out (Vojdani et al., 1992; Brautbar et al., 1995; Gedalia et al., 1995; Smith, 1995; Bar-Meir et al., 1995). Vojdani et al. (1992) have reported inhibition of mitogenic T-cell response, reduced lymphocyte capacity to eliminate tumoral target cells, an increase in antinuclear, antithyroid, anti-smooth muscle, antimyelin and antihistone immunocomplexes.

Cuellar et al. (1995) discovered 20 serum auto-antibodies in 116 women with silicone implants. They concluded that the implant had an "adjuvant" effect on immune response in 20% of these women. "The silicone serves as adjuvant and therefore might have an effect on immune tolerance... suggesting an atypical autoimmune disease" (Lewy and Ezrailson, 1996). ANA levels increased by between 30% and 57.8% depending on the antigen used. 55% of 500 women with silicone implants have autoantibodies (ANA performed using Hep-2 cells) compared to age-matched asymptomatic women (Bridges et al. 1996). Similar findings are published by Claman and Robertson (1996). Rowley et al. (1994), employed the ELISA method to demonstrate a significant increase in antibodies to collagen type 1 and compared these results with reactions to collagen type II which is more common in rheumatoid arthritis. T and B lymphocytes were identified by Sanger et al. (1995). However, consistent increases in immunoglobulins, C3 and fibrin levels were not observed.

Kossovsky et al. (1996) found elevated autoreactive antibodies to silicone surface in 310 symptomatic breast implants patients. These increased values allow a differential diagnosis to be made with other "classical" rheumatological disease.

Data suggesting potential silicone migration from capsules as an explanation for immune system impairment must be viewed with caution. Sánchez-Guerrero et al. (1995), in a study of 87,501 women with silicone implants over a period of 14 years, reported that silicone implants were not related to connective-tissue disease.

2) Granuloma formation. Reaction to foreign bodies

Chen (1995) and Truong et al. (1988) reported the highest frequency (24 and 9 cases respectively) of granulomatous reaction in axillary lymph nodes as a consequence of silicone injections (Chen, 1995) and silicone gel implants (Truong et al., 1988). Chen (1995) reported mastitis in 31% of cases and dermatitis in 16 %. Similar results were reported by Christie et al. (1977), Kircher (1980), Corrin (1982), Harvey and Leahy (1984), Dolwick and Aufdemorte (1985), Tabatowski and Sammarco (1992), Sammarco and Tabatowski (1992), and Emery et al. (1994).

Proximal or distal granulomatous reactions in tissue are induced by some form of silicone leakage from the implant, a finding highlighted by Del Rosario et al. (1995) who reported the presence of synovial-type metaplasia in 47% of patients studied. This, together with the granulomatous reaction mentioned earlier, could only be accounted for by leakage of silicone from implants.

Material and methods

A study was made of two women of 45 and 52 years of age who had received silicone gel breast implants after surgery for breast cancer. Four and six years later, respectively, they presented larger and painful homolateral axillary adenopathies with no other symptoms. Following histological diagnosis of silicone granulomatous lymphadenitis, non-ruptured implants were removed. However, there were signs of retraction, calcification, reddish and brittle tissue, as well as the presence of a biological pseudocapsule surrounding the implants.

Tissue extracts were fixed in 10% formol for routine histological analysis, embedded in paraffin and stained using H&E, PAS, Masson's trichrome stain, alcian blue and oil red (Shanklin and Smalley, 1996). The latter technique involved CO_2 freeze-slicing of sections obtained from formol-fixed samples. Fragments of lymph tissue from each patient were crushed for incineration using the Burriel method (Burriel et al., 1989). Platinum crucibles were placed for 30 min in a furnace at 550 °C for weighing and then transferred to a drier for a further 30 min. Two 5 gr aliquots from each crushed tissue sample were placed in each crucible. 150g/l magnesium acetate solution was added and gently heated to calcination point. The procedure was repeated and resulting ash represented 2% of sample tissue weight. 15 mg of tissue were removed and 15 mg of NaF and 12 drops of H_2SO_4 were added in a clean platinum crucible. The crucible was covered with cellophane upon which 4 drops of concentrated NaOH solution were placed and heated gently for 5 minutes. SiF_4 would result if any Si was present in the ash. As this is a volatile substance, it would form silicone on contact with the NaOH. The drops of NaOH were transferred to a platinum crucible and concentrated nitric acid was added until pH acidity was obtained. Ammonium molybdate was then added. The solution was gently heated and the liquid turned yellow as it formed a heteropolyacid. Once the solution had cooled, O-toluidine and sodium acetate were added. Blue coloration indicated the formation of molybdenum blue and therefore a positive identification of silicone in the calcinated biological samples.

Blanks were prepared with 15g of Na_2HPO_4 to which NaF was added and the same procedure followed as for the samples of ash. They were transparent after heating with molybdate and turned yellow when treated with O-toluidine.

Morphometric techniques

Case No.1

Different morphometric parameters were observed for spaces filled by silicone (vacuoles) (Table 1). 12 microscopic fields were analysed using x10 magnification which covered practically the entire surface area of lymph node sections. 1152 vacuoles were counted and measured in these 12 fields and considerable variation in form, size, area, perimeter, etc, were noted.

Case No.2

Different evaluation procedures were applied in this case. No silicone vacuoles were present but distant infiltration by foamy vacuolate histiocytes was observed. 6 microscopic fields constituting practically the entire surface area of lymph node sections were analysed at

Table 1. Silicone. Case 1. Objective lens 10x (6.3/0.2-NPL). Count: 12. Total number: 1152

	AREA (μm^2)	PERIMETER (μm)	CIRCULARITY (*)	LONG AXIS (μm)	Width (μm)	MEAN GRAY	STANDARD DEVIATION GRAY
Mean	14.30	97.29	1868.18	0.21	41.48	174.07	15.97
Maximun value	1341.33	3512.77	10345.81	3.32	774.11	212.54	38.13
Minimum value	0.12	5.34	200.27	0.01	2.63	79.68	2.53
Standard deviation	68.25	168.19	1434.91	0.28	53.17	15.23	5.39
Aritmetic mean	0.84	43.47	1348.38	0.09	20.78	172.61	13.77
Median	1.85	52.65	1362.26	0.12	25.63	175.73	15.93
Mode	0.25	21.04	1007.73	0.05	10.50	155.65	16.03
Variance	4658.31	28287.19	2058966	0.08	2826.91	231.91	29.03

(*): ArPerimeter x ArPerimeter/ArArea (perfect circle = 4π = 12.57).

Table 2. Case 2. Objective lens 2.5x (0.08 NPL).

	HISTIOCYTES		BACKGROUND		
	%H/B	Area	%H/B	Area	Total area
Field 1	30.04	28138.79	69.96	65525.22	93664.01
Field 2	19.15	17932.52	80.85	75731.49	93664.01
Field 3	18.99	1778.89	81.01	75875.13	93664.02
Field 4	17.91	16778.44	82.09	76885.57	93264.01
Field 5	8.52	7975.65	91.48	85688.37	93664.02
Field 6	26.63	24563.65	73.77	69100.36	93664.01
Mean	20.14	18862.99	79.86	74801.2	
Maximun value	30.04	28138.79	91.48	85688.37	
Minimum value	8.52	7975.65	69.96	65525.22	
Standard deviation	7.4884	6977.63	7.4484	6977.63	
Aritmetic mean	17.1675	16076.73	79.286	74263.27	
Median	19.07	17860.70	80.93	75803.31	
Mode	#N/V				
Variance	55.4796	486872395	55.4796	48687443.1	

x2.5 magnification. For each field, the space occupied by histiocytes was recorded and compared with remaining space in the tissue parenchyma ("back-ground"), as was the area of each of these portions, given that histiocyte shape and size were relatively uniform (see Table 2). Histiocytes represented on average 20.14% of total lymph node area (18862.99 μm^2) whereas lymph tissue accounted for 79.86% (74801.02 μm^2). Total field area was 93664.01, always set for x2.5 magnification.

All calculations were made using an image analyser running the Optimas (R) 5.2 programme and data was analysed using Microsoft Excel (R).

Results

Breast

In both cases, tissue surrounding the breast implant was involuted, with predominant stromal adipose. There was evidence of alterations in tissue surrounding silicone gel capsules, visible fibrous proliferation and giant foreign-body multinuclear cell granulomatous reactions; the presence of amorphous, crystalloid, non-staining material which was refringent and non-birefringent under polarised light and which did not stain when histological techniques were interpreted as silicone; these were subsequently confirmed by chemical analysis. Furthermore, microcalcifications were observed (Fig.1). Fibrosis and microcalcifications were more intense in case 2.

Lymph nodes

Alterations included rupture of some lymph node capsules, giving rise to fusion with adjacent lymphatic and connective tissue. In case No.1, lymph follicles were either incomplete or had disappeared completely. Histologically, there was evidence of extensive lymphohistiocyte infiltration, with occasional plasma cells, no eosinophils and occasional neutrophils. Vacuolate histiocytes formed granulomas, fusing to produce giant foreign-body-type multinuclear cells. The most striking feature, particularly in subcapsular tissue, was the presence of a large number of relatively

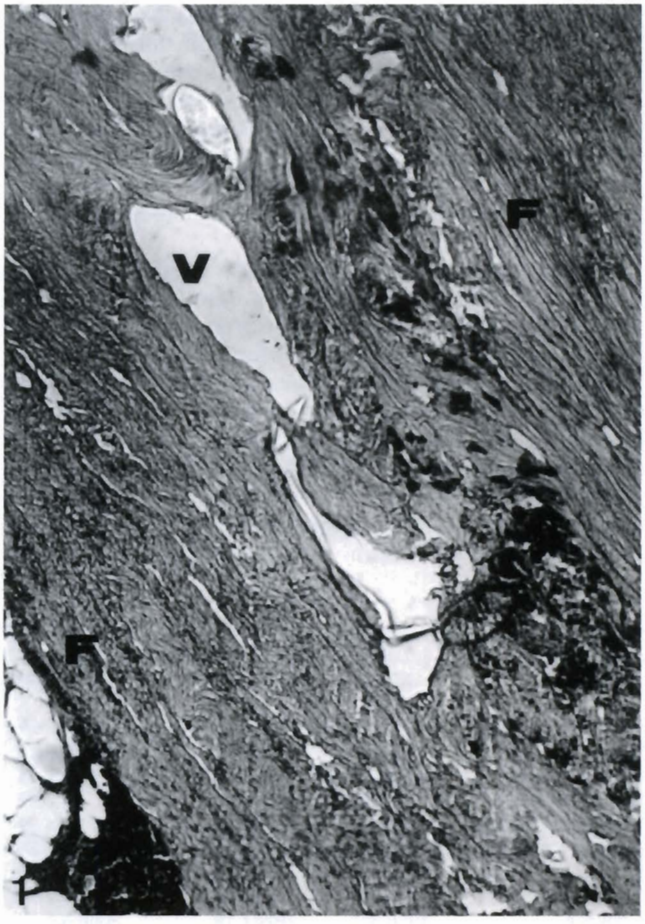

Fig. 1. Fibrosis (F), vacuoles of silicone (V) and microcalcifications. (Black stipple, arrow). Masson´s trichrome stain. x 75

well-defined empty spaces (vacuoles) of differing shapes and sizes (Table 1), which were negative to staining techniques including oil red (Fig. 2). Giant multinuclear cells (GMC) were most abundant around these spaces. Under narrow-aperture light microscopy (Koehler), these spaces were found to contain transparent, unstructured, refringent and non-staining material (Fig. 3). Material was occasionally crystalloid in appearance (Fig. 4, arrow). Similar observations were made in the cytoplasm of some histiocytes and giant cells and scattered throughout nodular or extracapsular stroma (refringent stippling in Fig. 4).

In case No.2, tissue alterations were observed but the vacuoles reported in case No.1 were not present. Numerous and occasionally vacuolate foamy histiocytes appeared, replacing part of the tissue parenchyma. Lymphocytes and incomplete lymph follicles were present throughout (Fig. 5).

2 and 3 years after removal of the silicone implants, patients were healthy and presented no local or distant symptoms. Blood biochemistry was normal.

Discussion

Histological findings in both cases were similar and typical granulomatous lesions secondary to silicone implant. No recurring cancerous tumors or implant-related reactions were observed in mammary glands (Daher et al., 1994; Petitg et al., 1994). No dysplasia was detected with the exception of a fibrogranulomatous reaction similar to that reported by Frey et al. (1992), Jansen et al. (1993), Emery et al. (1994), Friedman (1994), Laxenaire et al. (1994), Sanger et al. (1995), whose findings coincide with those of Sammarco and Tabatowski's study of lymph nodes (1992).

The present authors take issue with Jansen's criterion for defining clear vacuoles of granulomas, histiocytes and giant cells as "lipid" vacuoles, since the oil-red test employed in the present study and in other reported studies was negative.

Microscopic differences between the two cases, i.e. the predominance of histiocytes or vacuoles with giant cells, may be due to individual behaviour of implant

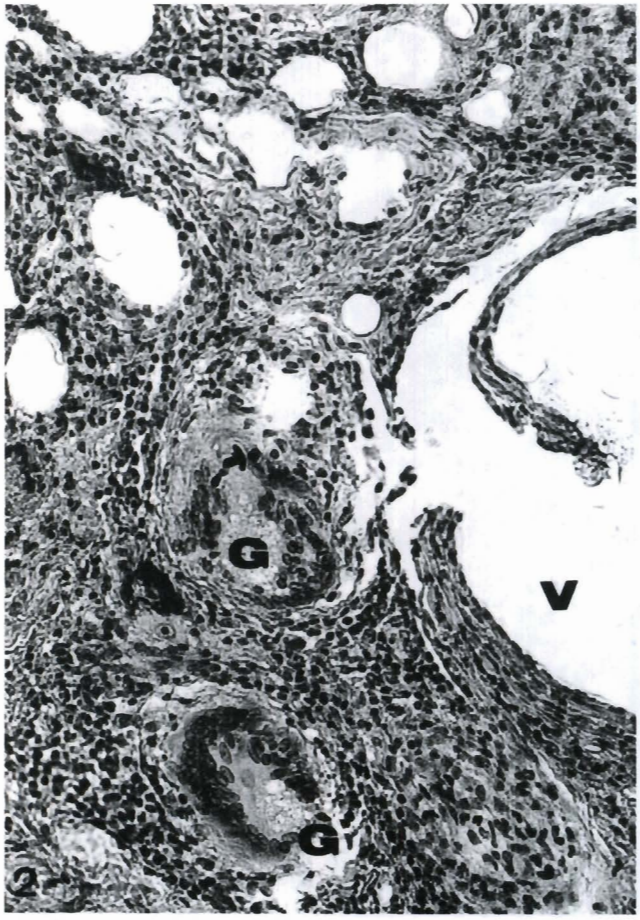

Fig. 2. Granulomatous reaction (G) and vacuoles of silicone (V) in the lymph node. H&E. x 75

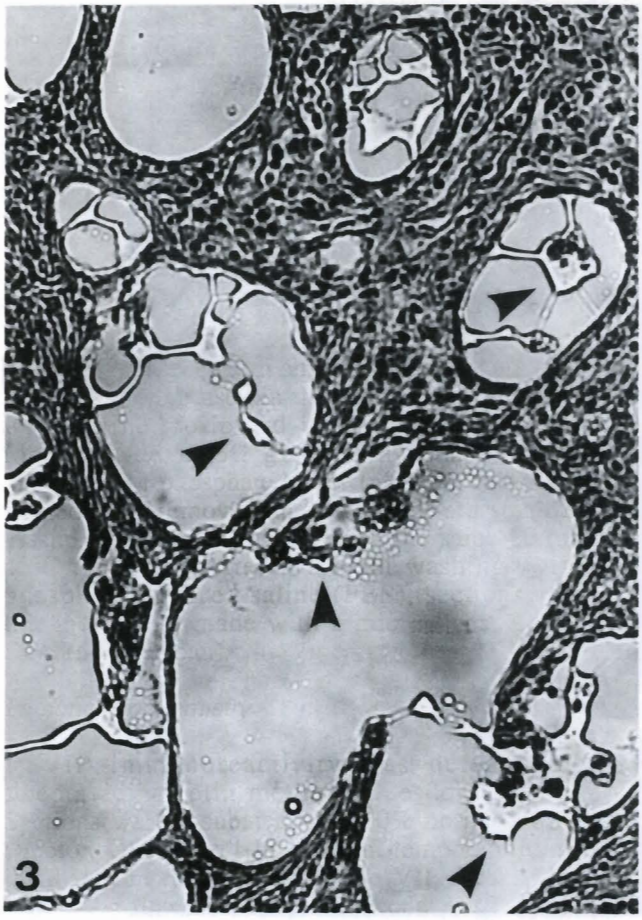

Fig. 3. Amorphous, refringent and non-staining material inside the vacuoles (arrows). H&E. (Koehler narrow-aperture). x 189

material or to differing foreign-body induced tissue reactions in the host.

Mammography in both cases was inconclusive. Similar data was collected in the 9 cases studied by Truong et al. (1988), where mammography revealed only one case of non-standard pathology.

Despite ongoing controversy in the literature regarding the risk of silicone implants, the cases presented here suggest that local (breast tissue) and distant granulomatous reactions (axillary lymph nodes) were caused by the leakage of implant material to surrounding breast tissue and subsequently to regional (axillary) tissue via the lymph system (histiocytic necrotizin lymphadenitis: Kikuchi's syndrome; Sever et al., 1996). These two cases can serve to confirm the possible "diffusion" of silicone ot the implan as reported by Brautbar et al. (1995).

Synovial metaplasia described by Emery et al. (1994) and Del Rosario et al. (1995) was not detected. Neither patient presented connective tissue anomalies of the sort associated with rheumatoid arthritis, lupus or scleroderma, as per the ACR criteria for the evaluation of these disorders.

Although histological analysis was not aimed here at determining the existence of silica, chemical analysis revealed its presence in the tissue samples studied.

This study did not seek to evaluate the complex and controversial immunological problems possibly induced by silicone implants (see Introduction). However, the authors agree with the biological principle argued by Granchi et al. (1995), that autoimmunity may result in capsular fibrosis; fibrosis increases with increased cytotoxic response to certain antigens (shown by measuring interleukins 2 and 6, TNF-alpha, and prostaglandin PGE2 obtained from pericapsular cell cultures). The hypothesis put forward by Peters (1995) of "special susceptibility" in some patients to the development of autoimmunity following silicone implants may find support in the "microdiffusion" of implanted silicone, although other aspects of this problem remain unknown.

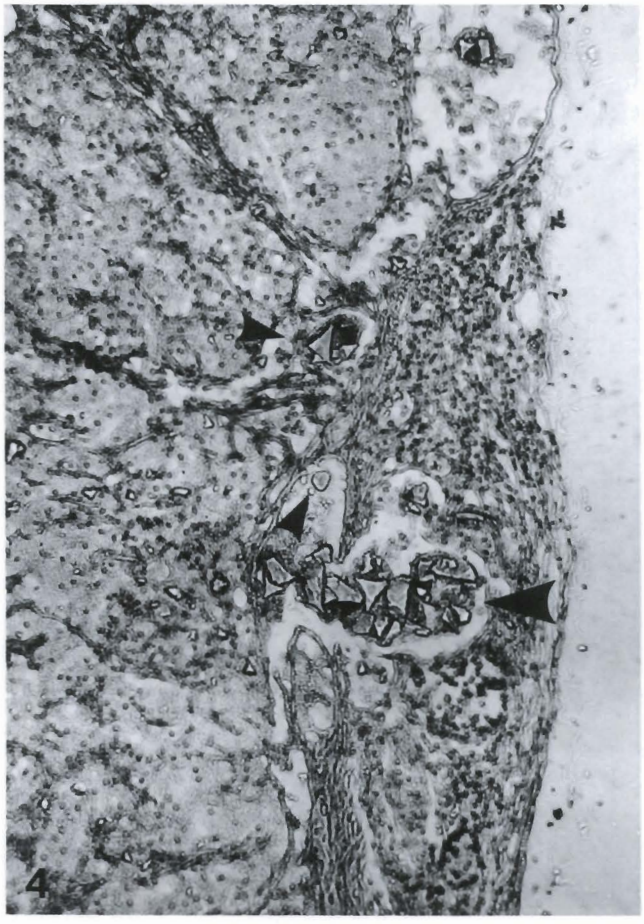

Fig. 4. Crystaloid material in the subcapsular and intersticial spaces and sinuses (arrows). H&E. x 300

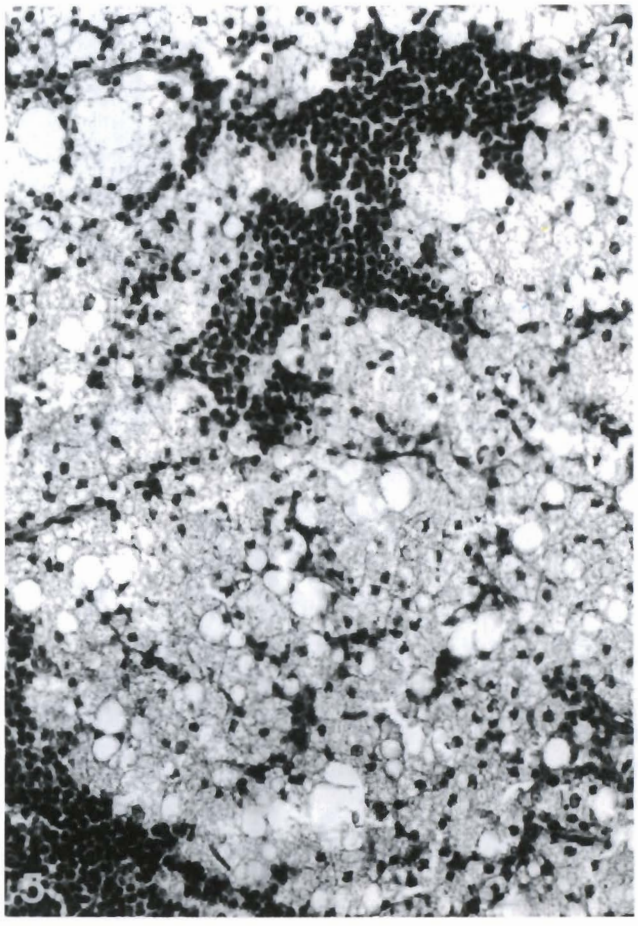

Fig. 5. Vacuolate histiocytes replacing lymphoid tissue. H&E. x 300

Conclusions

Chemical analysis, applied for the first time for silica detection in biological samples presenting this type of pathology, revealed the presence of silica in tissue surrounding breast implants and in homolateral lymph nodes. Similar findings were reported by Greene et al. (1995) using X-ray techniques for microanalysis. Given the possible biodegradation of silicone as reported by Brautbar et al. (1995), some mechanism must therefore exist whereby implant material leaks from the capsule, even though - as in one of the cases studied - the capsule is biluminal. Otherwise, it would be difficult to account for the clearly-demonstrated presence of silica in tissue surrounding the implant and, even more so, in regional lymph nodes.

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