

INTERSTITIAL LUNG DISEASES ASSOCIATED WITH METAL CONTENT IN SILICONE BREAST IMPLANTS: A CASE SERIES

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ABSTRACT. *Background:* Silicone gel-filled breast implants have been widely used for breast augmentation and reconstruction since the 1960's when the FDA approved them in women over 22 years of age. Concerns have been raised about the safety of those implants, with the focus upon whether silicone leak can spread to regional lymph nodes and remote organs and possibly cause inflammatory and immune responses. *Objective:* To present laboratory workup findings in 3 cases of interstitial lung diseases (ILD) linked with silicone implant leakage. *Methods:* ILD was diagnosed by tissue biopsy and Computerized Tomography (CT). We analyzed the metal content in both biological samples and raw material of the implants by means of scanning electron microscopy (SEM) and X-ray fluorescence (XRF). The metals lymphocyte proliferation analysis (MELISA[®]) was used to assess sensitization of the immune system to 19 metals. *Results:* The biological samples contained metals (silicon, nickel, zinc, tungsten, iron, aluminum, and zirconium) which are also present in the silicone implant. The MELISA test showed sensitization to nickel, zinc and tin. *Limitations:* Some of the immunogenic metals present in the implant were under the limits of detection of SEM and XRF and the sensitivity of MELISA test is unknown. *Conclusions:* The laboratory assessments of the 3 herein described women indicated that their interstitial lung disease was associated with the metal content of their silicone gel-filled breast implantations. (*Sarcoidosis Vasc Diffuse Lung Dis* 2018; 35: 381-389)

KEY WORDS: pulmonary disease; silicone; breast implant; metals

Acronyms and abbreviations

PFT, pulmonary function tests
SEM, scanning electron microscope
XRF, X-ray fluorescence spectrometer
ASIA, autoimmune/antiinflammatory syndrome

INTRODUCTION

Silicone implants are pre-filled with a thick, sticky gel elastomer that closely mimics the feel of human fat. Silicone breast implants have been an essential tool in the global plastic surgeon's cosmetic and reconstructive arsenal since their invention by Cronin and Gerow in 1962 (1), however, over 3% of the US female population are believed to have undergone silicone breast implantations. Silicone breast implants are not lifetime devices: their risk of rupture increases with age (2), with a 15% rupture rate at 10 years (3).

Despite changes in the principal constituents of the silicone implants during the past 50 years, silicone remained an agent prone to leakage and subse-

Received: 14 January 2018

Accepted after revision: 19 July 2018

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quently to become a chronic stimulus to the immune system resulting in similar clinical manifestations as recorded 50 years ago (4). Specifically, many studies on silicone breast implants showed adverse events such as autoimmune diseases occurring over 10 years after implantation (5), as well as a reappearance of silicone gel-filled breast implant toxicity (6). Breast seroma (7) and desmoid tumors (8) were suggested as being associated with the presence of silicone breast implants. Silicone lymphadenopathy associated with implantation of silicone breast implants is a foreign body reaction due to the release or migration of silicone into the tissues surrounding the breast implant (9,10). The appearance of silicone granulomas is another recognized complication of ruptured silicone breast implants (11).

Pulmonary disease has rarely reported to be linked to silicone breast implants (12), and only one case showed lung opacities in a study on 18 cases of silicone breast implant-induced lymphadenopathy (13). We reported the immunological response to gel elastomer material that was demonstrated by laboratory workup as being a causative agent of interstitial lung diseases (ILD) linked with silicone implant leakage in 3 cases.

METHODS

Study population

This case series includes 3 women with diagnosed ILD by lung biopsy and CT findings who developed systemic symptoms following the rupture of silicone breast implants.

Pulmonary function tests (PFT)

PFT were performed by a Masterlab spirometer (Masterlab E. Jaeger, Wurzburg, Germany). Measurements were carried out according to standard protocols of the American Thoracic Society/European Respiratory Society guidelines (14).

Sputum induction and processing

Sputum induction and processing were performed with an aerosol of hypertonic saline generated by an Ultrasonic Nebulizer – Model Omron U1

(Omron Health Care, USA) that has an output of 0.5 ml/min and particles with <5 μm aerodynamic mass median diameters (15,16). After separation of the plugs and viscous materials, all fractions of the induced sputum (IS) were preserved in 10% formalin and stored at 4°C until analysis of the mineral particles. We used the samples containing both extracellular and intracellular particles for the mineralogical analysis. The samples were treated with 14% formamide solution and filtered onto a 0.8- μm carbon coated Nuclepore filter (Millipore Filter Corp., Bedford, MA).

Mineralogical studies

Mineralogical studies were identified on the paraffin block of the lung/lymph node biopsy, the sputum sample or the gel elastomer. We used two devices: scanning electron microscope (SEM) X-ray analysis using a JEOL 840 SEM equipped with a Link 10,000 energy-dispersive system and X-ray fluorescence spectrometer (XRF) by a Niton XL3 XRF analyzer (Thermo Fischer Scientific, Munich, Germany) as previously described elsewhere (17,18),

MELISA test

MELISA[®] is an optimized lymphocyte transformation test that was described in depth elsewhere (19,20). Blood samples were drawn into tubes containing citrate for testing 19 selected metals (silica [SiO₂], nickel [NiCl₂], cobalt [CoCl₂], copper [CuSO₄], chrome [CrCl₃], aluminum [Al₂SO₄], titanium I [TiSO₄], titanium II [TiO₂], barium [BaCl₂], zirconium [ZrSO₄], tungsten [WO₃], molybdenum [MO₃], indium [In₂(SO₄)₃], manganese [MnCl], plumbium [Pb(NO₃)₂], mercury [HgCl₂], Gold Na₃Au(S₂O₃)₂], vanadium [VCl₃], and beryllium [BeSO₄]). The results were expressed as a stimulation index (SI), which is the ratio of the counts per minute of radioactivity in cells stimulated with metal salts divided by the counts per minute for unstimulated cells.

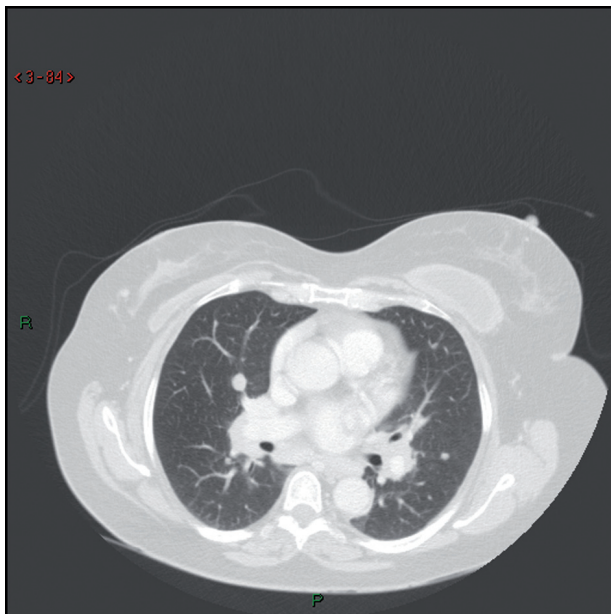
RESULTS

The 3 patients described below underwent breast augmentation with silicone gel-filled implant(s) in Israel.

Case 1

A 66-year-old woman was referred to our laboratory of pulmonary and allergic diseases due to cough and shortness of breath. She had undergone bilateral silicone gel-filled breast augmentation in 1999. In 2012, the implants were removed due to leakage. In 2014, she presented to our laboratory due to severe

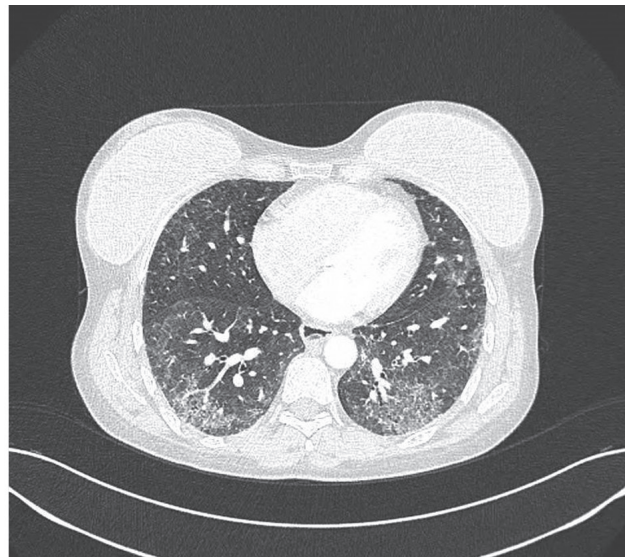
persistent cough and non-localized chest pain. PFT carried out in our laboratory demonstrated severe restrictive pattern with decreased diffusion capacity (Tables 1 and 2, Fig. 1). Her CT scan demonstrated hilar and mediastinal lymphadenopathy with enlarged axillary lymph nodes and multiple pulmonary nodules between 4-12 mm in size and distributed in the lung fields (Fig. 1). Bronchoscopy with transbronchial bi-



Case 1



Case 2



Case 3

Fig. 1. Computerized tomographic scans were evaluated for features indicative of interstitial lung disease

Table 1. Pulmonary function test findings for the 3 reported cases

PFT parameters % predicted	Case 1	Case 2	Case 3
FVC	60	55	45
FEV ₁	59.1	41	47
FEV ₁ /FVC	81.9	77	91
TLC	72	80	49
DLCO/SB	50	50	29
DLCO/VA	60	60	34

Pulmonary function tests were done by conventional methods (14) FEV₁, forced expiratory volume in 1s; FVC, forced vital capacity; TLC, total lung capacity; DLCO/SB, lung diffusion for CO/single breath; DLCO/VA, lung diffusion for CO/alveolar volume

opsy as well as surgical biopsy from the breast and axillary lymph nodes revealed non-necrotizing granulomatous inflammation. She was finally diagnosed as suffering of granulomatous lung disease treated with steroids according to acceptable protocol for granulomatous disease including sarcoidosis: prednisone 40 mg/day tapering down during 6 months with partial clinical improvement (Table 2).

Case 2

A 31-year-old woman had undergone a left silicone gel-filled breast implant at the age of 19 years because of breast asymmetry. Her past clinical history was unremarkable, and she denied any family history of autoimmune diseases. Five years later, she started to complain of weakness, diffuse chest and abdominal pain, nausea, intermittent diarrhea and weight loss. A leak in the implant was confirmed by CT and it was replaced with another silicone gel-filled implant. She complained of shortness of breath

for two years, during this time she was treated with inhaled budesonide which didn't help for presumptive diagnosis of asthma. The second implant was removed in 2013, again due to leakage. PFT findings demonstrated severe restrictive pattern with decreased diffusion capacity. She underwent another CT scan and bronchoscopy the results demonstrated diffuse micro-nodules on both lung fields with a ground glass appearance leading to the clinical pathological diagnosis of NSIP (Tables 1 and 2, Fig. 1). Then, she continued treatment with prednisone 40 mg/day with tapering down.

Case 3

A 47-year-old woman who had undergone a silicone breast implant 12 years earlier complained of progressive cough and dyspnea for the past 2 years. Past history was remarkable for celiac disease and esophageal dysmotility with Raynaud phenomenon. Her serological evaluation for scleroderma was negative. PFT revealed a severe restrictive pattern with decreased diffusion capacity. Her CT scan demonstrated diffuse interstitial and reticular ground glass changes with peripheral and basal predominance (Tables 1 and 2, Fig. 1). She was diagnosed with COP and treated with prednisone 40 mg/day with tapering down during 6 months and azathioprine as steroid sparing agent, during this time her condition deteriorated and she was listed for lung transplantation.

For all three cases we excluded tuberculosis in all three patients by performing Broncho-alveolar lavage for AF stain, TB culture and TB-PCR test.

Table 2. Computerized tomographic scans¹ and histology findings² of the 3 patients

Diagnostic method	Case 1	Case 2	Case 3
Left axillary lymph node	Granulomatous lymphadenitis		
Open lung biopsy	Sarcoidosis, silicone exposure	Interstitial inflammation with marked intra-alveolar pigmented macrophage accumulation	Diffuse alveolar damage with cellular interstitial organizing pneumonia.
CT findings	Mediastinal lymphadenopathy, bilateral diffuse alveolar opacities	Bilateral diffuse alveolar opacities with homogenous distribution	Diffuse interstitial and reticular ground glass changes with peripheral and basal predominance.

¹Evaluated for features indicative of interstitial lung disease. ²Findings on the paraffin block of the lung biopsy.

ANALYSES OF BIOLOGICAL AND ELASTOID SILICONE GEL SAMPLES

All 3 cases were referred to our laboratory for a comprehensive study to determine a possible causative agent of the lung disease as well as a possible link between it and rupture of the silicone implants. Analysis of the biological samples was done in tissue samples in all 3 cases, as well as in the IS sample in one of them. In the latter case, the results of the SEM analysis of the silicone gel, tissue and sputum

were superimposed in order to inspect any similarity of the mineral contents display among the 3 samples (Fig. 2). A wide range of metals was identified in all the samples when the analyses were performed by both SEM (which measures only selective points of the sample) and XRF (which measures the entire surface of the sample) (Table 3, Fig. 3). The analysis in the gel elastoid was performed in the 2 cases in which the implant was explanted. The results of both the SEM and XRF analysis demonstrated the presence of silicon, while XRF identified others met-

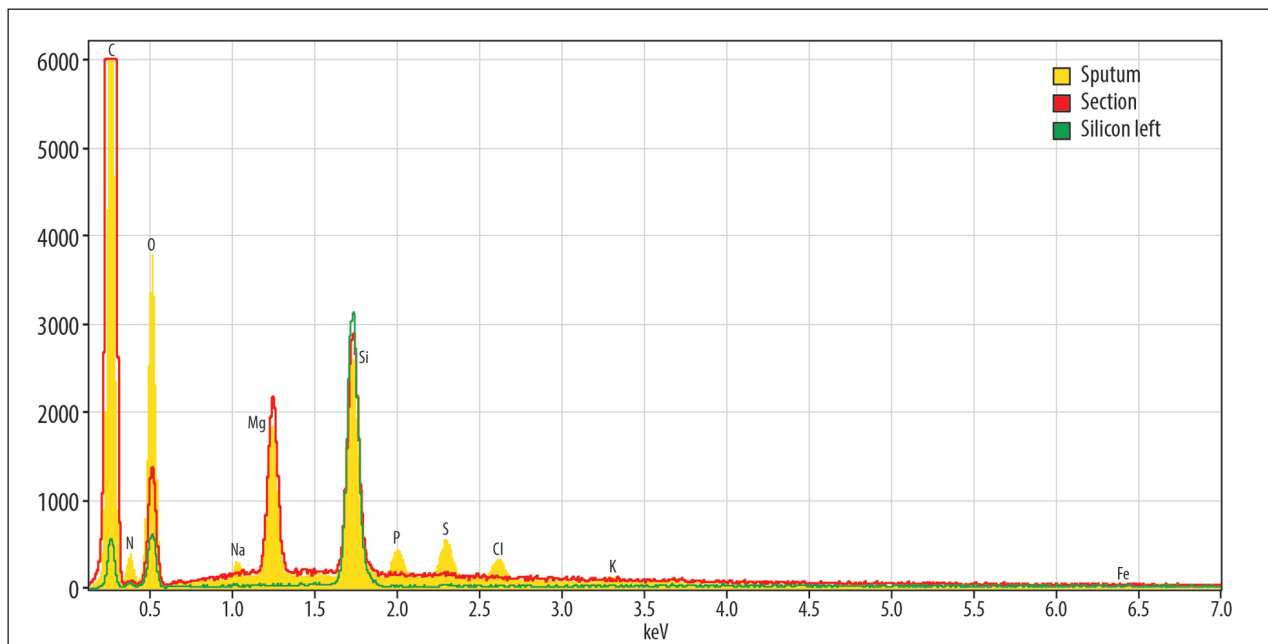


Fig. 2. Three spectra superimposed: sputum sample (yellow), lung section (red) and silicon implant raw material (green)

Table 3. Identification of metals by SEM and XRF

	SEM	XRF
Case 1		
Shell of the implant	Si	Si, Cd, Mo, Zr, W, Al, Zn, Ni, Fe, Cu
Lymph node	Si, Ni, Zn, Co, W, Cr, Cu, Mn	NA
Lung biopsy	Si, Fe, Al, Cr, Ti	Co, Cr, Fe, Zn, Ni
Case 2		
Shell of the implant	Si	Si, Cd, Mo, Zr, Cu, W
Induced sputum	Si, Fe, Al, Cr, Au, Ni	NA
Lung biopsy	Si, Fe, Au, Ni, Cr	NA
Case 3		
Shell	NA	NA
Lymph node	NA	NA
Lung biopsy	Si, Al	Si, Ni, Mo, Zr, W, Cu, Co, Fe, Ti

Al, aluminum; Cu, copper; Si, silica; Fe, iron; Ti, titanium; Cr, chrome; Ni, nickel; Au, gold; Mo, molybdenum; Zn, zinc; Mn, manganese; Co, cobalt; W, tungsten; SEM: scanning electron microscope; XRF: X-ray fluorescence.

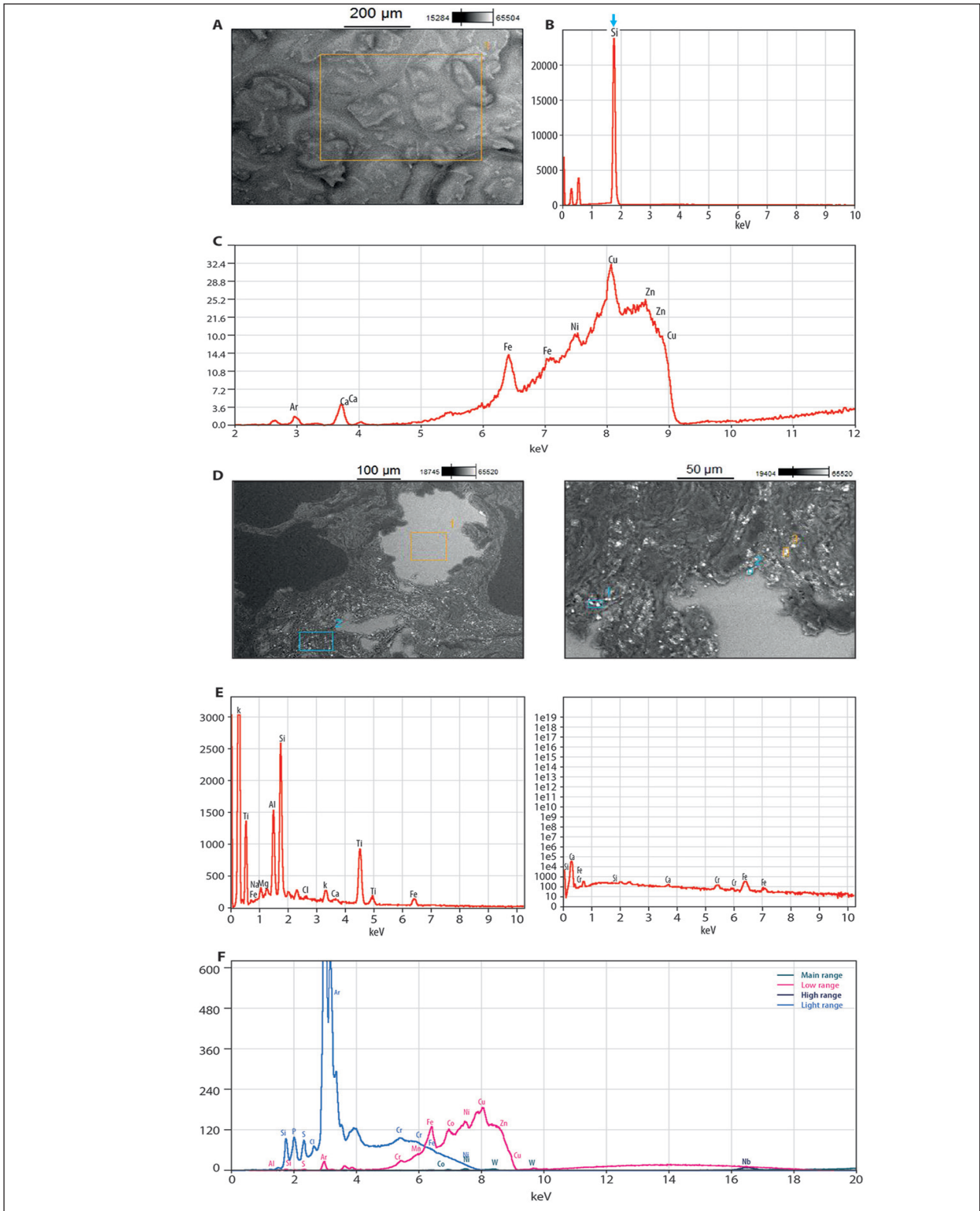


Fig. 3. Representative analysis by samples. **A.** Picture and **B.** spectra of shell gel elastoid by SEM in Case 1. **C.** Picture and **D.** spectra of biopsy by SEM and **E.** XRF of Case 2

Table 4. Results of positive proliferative response of lymphocytes to metals: metals lymphocyte stimulation (MELISA) assay

Case 1	Case 2	Case 3
Nickel	ND	Nickel
Tin		
Zinc		

MELISA was performed as described in Materials and Methods
ND, not done

als (cadmium, molibden, zirconium, tungsten, aluminum, zinc, nickel, iron, and cuprum).

METALS LYMPHOCYTE STIMULATION ASSAY

Since the presence of metals in the biological samples *per se* does not demonstrate a causative link between pulmonary disease, we performed the metal lymphocyte proliferation test (MELISA) in 2 compliant women in this series. The test was positive for nickel, zinc and tin in Case 1 and for nickel in Case 3 (Tab. 4).

DISCUSSION

Health risk and safety concerns of silicone gel-filled breast implants and the more common complications associated with them include local inflammatory reactions, autoimmune reactions and the migration of silicone fluid to the axillary nodes. They are the subjects of controversies that have remained unresolved for decades (21). The determination of whether a possible exposure is risky and what is the likely risk is by observational epidemiologic studies. In one such study, the relative risk and association between silicone implants and connective tissue disease was measured by means of data retrieved from questionnaires among a cohort of 87,500 women (22). A meta-analysis of a large group of studies investigated the possible relation between silicone breast implants and the risk of autoimmune conditions or connective tissue diseases (23). Neither of those 2 studies showed any evidence of silicone as being the causative agent of those disorders. It should be borne in mind that these kinds of studies are difficult to interpret, and that confounding variables are almost always present but not always adequately accounted for or even identified. Moreover, most of those studies focus on the link between silicone implants and

autoimmune diseases, while few consider a possible link to pulmonary conditions. In a retrospective review of cases of silicone-induced lymphadenopathy after breast implant encountered at Mayo Clinic in Rochester between 1998 and 2008, there were 18 cases of silicone-induced lymphadenopathy (axillary, supraclavicular, internal mammary, and mediastinal), but only one patient was found to have pulmonary opacities (24). Another case series described 4 women who had undergone silicone implants breast augmentation as being diagnosed with autoimmune/antiinflammatory syndrome (ASIA) with pulmonary infiltrations (25). The authors of that report argued that the immunological reaction should be caused by adjuvants including silicone and vaccines but they provided no laboratory workups to show a direct link between the materials contained in silicone implants and ASIA. Moreover markers of autoimmune diseases were assessed only in one case out of the four cases described in the report as this workup was only considered a minor criteria for the diagnosis of ASIA. In this context we did not include those markers in our work-up (25).

We believe that this is the first report on the analysis of the metal content of elastoid silicone gel extracted from breast implants. The data provided by the U.S. Department of Health and Human Services Food and Drug Administration Center for Devices and Radiological Health in 2006 (26) showed that metals are used as the catalyst in the curing reaction, and that they are present in the final finished gel elastoid. The heavy metals that are most commonly present are platinum, tin, zinc, chromium, arsenic, lead, antimony, nickel, and copper.

We measured the metal contents in both the silicone implants and in the biological samples (tissue and sputum) in order to investigate the possibility that there may be an association between the silicone implants and interstitial lung diseases. The implants that were explanted in 2 of the 3 women in the current series were made available to us for analysis of metal content, and our analysis showed the presence of metals. The FDA approval granted to the manufacturer of all the implants in the current report noted that there is a wide range of heavy metals in "trace ranges" in the gel elastoid (27). It is well documented, however, that exposure to even very low sub-toxic exposure to concentrations of heavy metals which are considered as "safe" levels are sufficient

to affect the immune system (i.e., endothelial cells, epithelial cells, and alveolar macrophages) as well as the respiratory tract (28-32). Metal dusts and fumes can induce a wide range of lung pathologies, including airways disorders, cancer, and, especially, parenchymal diseases such as granulomatous lung disease, giant cell interstitial pneumonitis, chemical pneumonitis, and interstitial fibrosis (33). Although the route of entrance and the sensitization to the metals in our 3 reported cases was not by inhalation, antigens can be introduced into the immunological system by other organs, such as the skin (34). In this context, we demonstrated sensitization to beryllium in a patient with "sarcoidosis" by a piece of shrapnel which contained aluminum and beryllium which was embedded in his chest (35). Two case reports described the use of silicone in cosmetics that induced granulomatous pneumonitis (36, 37).

The presence of the metals in tissue is crucial to show causation, but further linkage to disease requires the demonstration of individual sensitization to those metals. The use of the beryllium lymphocyte proliferation tests (LPT) in medical surveillance identified beryllium sensitization at low exposures with chronic beryllium disease that led to physiologic impairment and the need for immunosuppressive medications (38). Moreover, it was recently shown that LPT can be useful in assessing occupational sensitization (39). Several case reports demonstrated increased lymphocyte proliferation to titanium (40), aluminum (41), chromium and nickel (42), the latter as a side effect following hip arthroplasty. We recently conducted a pilot study whose results determined that MELISA is effective in identifying sensitization to a number of selected metals in a cohort of sarcoid patients with lung granulomatous diseases who had been exposed to various substances at the workplace and in the environment (43). We found that 2/3 of our cases showed sensitization to nickel and 1/3 to tin and zinc. Lymphocyte transformation testing has often been used as an *in vitro* test for nickel sensitization (39-44), and prolonged exposure to a prosthesis containing nickel and titanium was speculated to have triggered the symptoms of systemic auto-inflammation, alluding to ASIA induced by adjuvants (45). It is also known that metals, such as chromium, nickel, platinum, and zinc, have notable antigenic properties, that they induce cell-mediated responses, and that they cause immunologic lung and skin diseases (29, 46).

This study has some limitations. First, metal content was analyzed by SEM and XRF in order to enhance metal detection sensitivity, but some immunogenic metals that were present in the implant may have been under the limits of detection. Secondly, the salts of the metals used in the MELISA test may not have been those with high immunogenic properties for these specific patients, in which case there might have been false-negative results.

In summary, in our knowledge we present the first evidence-based verification of elastoid silicone gel implant-induced lung disease with 3 women. The prevalence of pulmonary sequelae associated with metals may be under-reported. Increased awareness and targeted laboratory investigation may reveal greater numbers of recipients of silicone gel implants with undiagnosed or incorrectly diagnosed lung pathologies.

ACKNOWLEDGMENT

Esther Eshkol is thanked for editorial assistance.

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