Pathology of Lymph Nodes From Patients With Breast Implants

A Histologic and Spectroscopic Evaluation

William E. Katzin, MD, PhD,* José A. Centeno, PhD,† Lu-Jean Feng, MD,‡ Maureen Kiley, MS,† and Florabel G. Mullick, MD†

Abstract: There are only a few published reports describing the pathology of regional lymph nodes from patients with silicone breast implants. Systematic analytical chemical verification of foreign material has not previously been reported. In this study, biopsies of regional lymph nodes from 96 patients with breast implants were studied using conventional histology as well as laser-Raman microprobe spectroscopy and Fourier transform infrared microspectroscopy. Lymph nodes from 12 patients without implants served as negative controls. Foamy macrophages, ranging from rare scattered cells to confluent sheets, were observed in sections of lymph nodes from 91 patients with implants and only rare foamy macrophages were observed in sections from 4 patients without implants. Refractile material consistent with silicone was observed in sections from 86 patients with implants and in no sections from patients without implants. Fragments of foreign material consistent with polyurethane were observed in sections from 16 patients with implants and in no sections from patients without implants. Using spectroscopy, the presence of silicone was confirmed in 71 patients with implants, and the presence of polyurethane was confirmed in 2 patients with implants. Spectroscopy was negative for silicone and polyurethane in all patients without implants. In summary, regional lymph nodes from patients with breast implants often have histologic evidence of silicone migration. Characteristic histologic findings include foamy macrophages and refractile droplets of clear material. Polygonal fragments of polyurethane were observed in lymph nodes from a number of patients. This finding has not been previously reported. The presence of silicone and polyurethane was confirmed using confocal laser-Raman microprobe and Fourier transform infrared microspectroscopy. Other than two prior case reports, this is the first confirmatory evidence of silicone migration to lymph nodes in patients with breast implants and this is the first confirmatory report of polyurethane migration to lymph nodes.

Silicone gel-filled breast implants have been used for breast reconstruction following mastectomy and for breast augmentation for more than 40 years. These prostheses have undergone a number of modifications over time, mostly in an attempt to optimize the cosmetic result. The original Cronin implant had a relatively thick shell and its contents were a highly viscous gel, resulting in a relatively firm breast. The introduction of the thin-walled shell and a more fluid gel was reported to improve the consistency of the surgically modified breast. However, long-term follow-up of many of the patients who had the revised implants disclosed a relatively high frequency of capsular contracture, a complication consisting of rubbery firmness and, in some cases, visible distortion of the breast. Polyurethane-coated implants were introduced in 1970 in an attempt to prevent capsular contracture.[2]

Silicone gel can escape from its confines within the silastic envelope and can be deposited in the fibrous tissue or capsule that forms around a breast implant. The identity of silicone in the capsular tissue has been confirmed by a number of analytical methods including Fourier transform infrared (FTIR) spectroscopy,[15,28] laser-Raman spectroscopy,[17] and gas chromatography/mass spectroscopy.[34] By light microscopy, silicone within the capsule appears as droplets of refractile, unstained material.[47] With time, the polyurethane film coating implants typically degrades and can also become embedded in the capsular tissue.[16,57,58] Particles from the polyurethane coating typically appear as polygonal fragments of refractile material.[16,31] The identity of polyurethane in capsular tissue has also been confirmed using FITR spectroscopy.[16]

Morphologic changes in regional lymph nodes from patients with silicone breast implants, collectively designated silicone lymphadenopathy, were first described in 1978 by Wintsch et al,[65] Hausner et al,[29] and Capozzi et al.[14] They all noted the presence of vacuoles and pseudocysts containing refractile, nonstaining, nonpolarizable material, presumably silicone, in a cellular background that contained histiocytes and multinucleated giant cells with vacuolated cytoplasm. More recently, there have been additional case reports,[30,35,39,41,42,48,49,53,54,60,62] and in 1988 Truong et al[61] reported

From the Departments of *Pathology and ‡Surgery, Case Western Reserve University School of Medicine, Cleveland, OH; and †Department of Environmental and Infectious Disease Sciences, Armed Forces Institute of Pathology, Washington, DC.
Reprints: William E. Katzin, MD, PhD AmeriPath-Cleveland, 7730 First Place, Suite A, Oakwood Village, OH 44146 (e-mail: wkatzin@ameripath.com).

a series of 9 cases of silicone lymphadenopathy involving patients with breast implants. In addition to describing the histologic features, they also used energy-dispersive x-ray elemental analysis to confirm the presence of the element silicon in 7 of their cases. In 1995, Kulber et al[38] reported a series of 23 patients with silicone implants who had palpable axillary lymphadenopathy and who subsequently underwent axillary lymph node biopsy. In addition to changes of silicone lymphadenopathy that were seen in all of those patients, 7 of those patients also had metastatic breast cancer. The histologic features of silicone lymphadenopathy were only briefly discussed in that report. To our knowledge, the presence of molecular silicone in regional lymph nodes of patients with breast implants has been confirmed spectroscopically in only two prior case reports.[35,65]

In this report, we describe the histologic features of silicone lymphadenopathy in regional lymph nodes from a large series of patients with silicone breast implants. Included in this series are a significant number of patients with polyurethane-coated breast implants. We found fragments of polyurethane in lymph nodes from 16 different patients. Confocal laser-Raman microprobe (CLRM) and FTIR were both used to confirm the presence of silicone and polyurethane in sections from the lymph nodes.

MATERIALS AND METHODS

Case Materials

The study was based on an evaluation of lymph nodes from 96 patients with silicone gel-filled breast implants and 12 "control" patients without implants. In almost all of the patients with implants, lymph nodes potentially containing silicone were identified by ultrasound. Lymph node biopsies were performed in these patients based on their concern about possible adverse effects of silicone on their health and their desire to remove all residual silicone following implant removal. In some cases, the patients complained of axillary tenderness. All patients were female. The patients with implants ranged in age from 29 to 66 with a mean age of 47.5 years (SD = 8.1 years). A significant number of the patients with implants had multiple sets of implants. The time from insertion of the first known implants to lymph node biopsy in these patients ranged from 1 year to 30 years. The median period of time that the patients had implants was 11 years (mean, 12.2 years). In all of these patients, the silicone implants were removed either prior to or at the same time as the lymph node biopsy. In 47 (49%) of these patients one or both of the implants had visible evidence of rupture. Axillary, internal mammary/intercostal, retropectoral, rotter, supraclavicular, intramammary, and abdominal wall lymph nodes were biopsied from patients with implants: 86% of those were from the axilla. The control patients ranged in age from 32 to 75 with a mean age of 49.9 years (SD = 12.1 years). Nine of 12 of the control patients had axillary lymph node biopsy for staging of breast cancer. One of the control patients had an intramammary lymph node biopsy at the time of surgery to rule out local recurrence of breast cancer. One of the control patients had a lymph node biopsy at the time of breast

reconstruction surgery following mastectomy for breast cancer. The final control patient had a lymph node biopsy at the time of breast reduction surgery. Axillary, internal mammary, and intramammary lymph nodes were biopsied from control patients: 88% of those were from the axilla. Lymph nodes were fixed in neutral-buffered formalin and embedded in paraffin using a tissue-Tek VIP processor that included dehydration through graded alcohol and xylene.

The patients with silicone breast implants had a variety of different types of prostheses. Many patients had multiple sets of different types of implants. The types of implants removed at the time of lymph node biopsy (or the most recent types in patients who had prior implant removal) were as follows: single lumen, smooth surface gel (n = 29); single lumen, smooth surface saline (n = 1); single lumen, textured surface gel (n = 5); single lumen, textured surface saline (n = 7); single lumen gel with Dacron patch (n = 6); single lumen gel with polyurethane coating (n = 36); and double lumen, smooth surface (n = 6). In 1 patient the right and left implants were different types and in 7 patients the type was unknown. Device manufacturers included Dow Corning, Heyer-Schulte, Mentor, McGhan, Aesthetech, Cox-Uphoff, Medical Engineering Corporation/Surgitek, and Bristol-Myers Squibb.

Light Microscopy

Four- to six-micron sections were stained with hematoxylin and eosin. The presence and degree or absence of the following histologic features were assessed: 1) foamy macrophages (estimate of the percent area of the node effaced); 2) plasma cells (absent, present, or marked); 3) sarcoid-like granulomas (absent, present, or marked); 4) giant cells (absent, present, or marked); 5) follicular hyperplasia (follicles absent, follicles present, follicular hyperplasia); 6) sinus histiocytosis (absent, present, or marked); 7) refractile material morphologically consistent with silicone (absent, present, or marked); and 8) refractile material morphologically consistent with polyurethane (absent or present). Slides from a total of 361 paraffin blocks were evaluated including 35 from the control patients. To achieve consistency, the histologic evaluation in all cases was performed by a single observer (W.E.K.) and was conducted in a blinded fashion, without knowledge of the name or implant status of the patients (all data were initially recorded according to the surgical pathology accession number).

Microspectroscopy of Lymph Node Tissues

CLRM was performed on sections from lymph nodes using a LabRam spectrograph (JY Hobira and Dilor, France). The instrument is equipped with a He:Ne laser having an excitation wavelength of 632 nm. The optical unit permits ordinary light viewing as well as illumination of the sample by laser light. A high stability BX 40 Olympus microscope was used: 10×, 50×, and 100× objectives were used to view the sample using ordinary light and the 100× objective was used to collect Raman spectral images. The confocal characteristics of the microscope were provided by an adjustable confocal hole (range, 100–1000 μm), which allows for reduction of stray light and laser plasma lines. The spectrograph consisted of two gratings mounted on the same shaft blazed at 1800 grooves/nm (holographic) and 950 grooves/nm, and

a charge-couple detector with an active detector window of 1024 × 256 pixels. This instrument when interfaced with the BX 40 Olympus microscope is capable of providing spatial resolution of approximately 1 μm. FTIR microspectroscopy was conducted employing a Nicolet instrument (Model micro-IR FTIR). The spectroscopic analysis was also conducted without knowledge of the implant status of the patients.

RESULTS

In patients with silicone gel-filled breast implants, the general lymph node morphology varied from one case to another. In some lymph nodes the architecture was preserved, whereas in others there was nearly complete effacement of the normal lymphoid tissue. In most cases, there was at least a minor degree of sinus histiocytosis. Prominent follicular hyperplasia was uncommon. Regional lymph nodes from patients with silicone breast implants frequently contain foamy macrophages: cells with relatively abundant, finely vacuolated cytoplasm (Fig. 1). Foamy macrophages were identified in 294 of the 326 sections of lymph nodes from 91 of the 96 patients with breast implants. The number of foamy macrophages varied greatly from only a few rare cells to confluent sheets of cells that extensively replaced the normal lymphoid tissue. In the patients with implants, the average area of the lymph node replaced by foamy macrophages was 24%. Rare, isolated foamy macrophages were seen in only 5 of the 35 sections of lymph nodes from 4 of the 12 control patients without implants. Multinucleated giant cells (Fig. 2), sometimes associated with large vacuoles, were seen in 135 of the 326 sections of lymph nodes from patients with implants and in none of the sections from the controls. Refractile droplets of unstained foreign material consistent with silicone (Fig. 2) were seen in 267 of the 326 sections of lymph nodes from 86 of the 96 patients with implants and in none of the sections from the controls. Tiny droplets of refractile material were sometimes noted in the fine vacuoles of foamy macrophages. Larger droplets or irregular fragments of refractile material were generally present in large vacuoles that may or may not have been associated with multinucleated giant cells. The presence of sarcoid-like granulomas (Fig. 2) was an infrequent histologic finding, seen in only 6 sections of lymph nodes from 5 patients with implants and in none of the sections from control patients. Prominent sinus histiocytosis was present in 52 sections of lymph nodes from patients with implants and in none of the controls. Fragments of foreign material consistent with polyurethane (Fig. 1) were seen in 33 sections of lymph nodes from 16 different patients with implants. All but 2 of those patients were known to have polyurethane coated implants. Those 2 remaining patients had multiple sets of implants, some of unknown type. The presence of polyurethane was confirmed spectroscopically in both of those two patients. Polyurethane fragments were not seen in any of the control sections. Prominent plasmacytosis was seen in only three sections from 2 different patients, both with implants. Prominent follicular hyperplasia was seen in 15 sections, all of lymph nodes from patients with implants.

CLRM and/or FTIR spectra characteristic of silicone (Fig. 3) were observed using sections from 191 of the paraffin
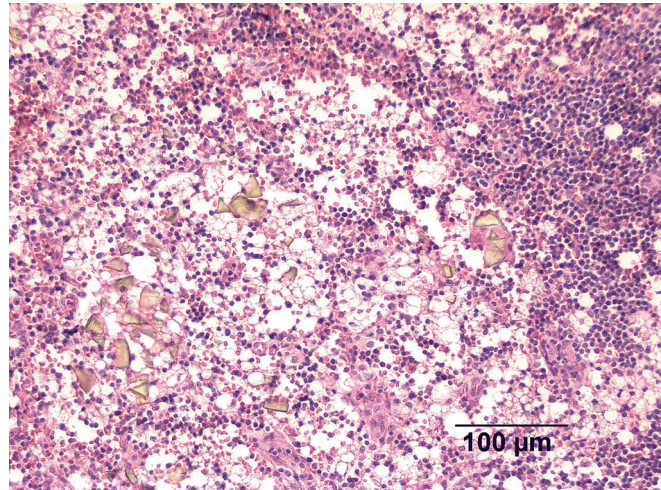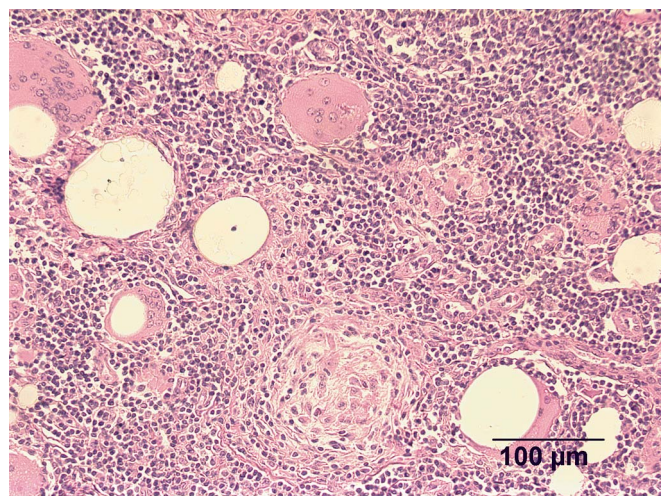

FIGURE 1. Photomicrograph of a lymph node from a patient with breast implants showing foamy macrophages and scattered multinucleated giant cells. Silicone containing vacuoles vary in size. There are multiple polygonal fragments of refractile foreign material consistent with polyurethane (original magnification ×200).

blocks of lymph nodes from 71 of the 96 patients with breast implants. None of the control lymph nodes was positive for silicone. CLRM spectra characteristic of polyurethane (Fig. 3) were observed in sections from two paraffin blocks of lymph nodes from 2 different patients with breast implants and in none of the control lymph nodes.

DISCUSSION

Patients with silicone gel-filled breast implants may have histologic and spectroscopic evidence of silicone in regional

FIGURE 2. Photomicrograph of a lymph node from a patient with breast implants showing frequent multinucleated giant cells, some associated with vacuoles containing refractile material consistent with silicone gel. A sarcoid-like granuloma is also present (original magnification ×200).
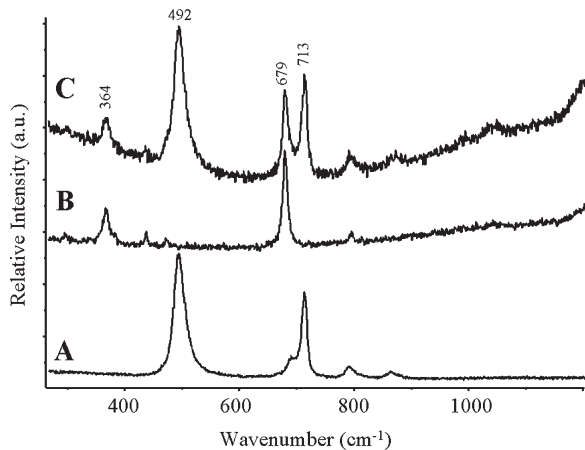
FIGURE 3. Raman microprobe spectra of polydimethylsiloxane (PDMS, bottom trace) and polyurethane (PU, top trace) inclusions in a lymph node from a patient with polyurethane-coated implants. PDMS spectral contributions are identified at 492 and 712 cm^{-1}, while the characteristic PU peaks are seen at 363 and 678 cm^{-1}. The experimental parameters were: laser line at 632 nm, resolution at 2 cm^{-1} (original magnification at ×100).

lymph nodes. The large number of patients in this study indicates that this phenomenon is not rare. Histologic features that are frequently present include partial replacement of the lymphoid tissue by foamy macrophages, the presence of refractile unstained amorphous material consistent with silicone, and multinucleated giant cells that are often associated with large vacuoles. Based on the observation of rare foamy macrophages in lymph nodes from 4 of the control patients, the effacement of at least 5% of the area of a lymph node by foamy macrophages is proposed as a histologic criterion for the diagnosis of silicone lymphadenopathy. Admittedly, this cutoff is somewhat arbitrary and in patients with a known history of silicone gel breast implants, even a few scattered foamy macrophages should be considered suggestive of the diagnosis. Based on the 5% cutoff, 84% (81 of 96) of the patients with implants had histologic evidence of silicone lymphadenopathy. Refractile, clear material was not observed in any of the sections from control patients, and therefore, in patients with a known history of silicone gel breast implants, this is another reliable criterion for the diagnosis of silicone lymphadenopathy. This feature was observed in histologic sections from 90% (86 of 96) of the patients with implants. There was only 1 patient with greater than 5% foamy macrophages in whom refractile material was not seen; therefore, using either criterion, a total of 91% (87 of 96) of the patients with implants had histologic evidence of silicone lymphadenopathy.

Patients with polyurethane-coated breast implants may have polygonal fragments of degraded polyurethane foam in regional lymph nodes. Polyurethane fragments were identified in lymph nodes from 14 (40%) of the 35 patients known to have polyurethane-coated implants. This finding has not been previously reported, although a photomicrograph in the case report by Vaamonde et al[62] illustrates a particle within a lymph node that is probably polyurethane.

The presence of silicone was confirmed in 74% of the patients using CLRM and/or FTIR-microspectroscopy. Spectroscopic confirmation of molecular silicone in lymph nodes from patients with breast implants has been reported previously in only 2 patients.[35,65] Using energy dispersive x-ray elemental analysis, Truong et al[61] found elemental silicon in 7 patients with silicone lymphadenopathy as did Tabatowski et al[60] in 1 patient. McConnell et al[41] also confirmed the presence of elemental silicon in 1 patient with silicone lymphadenopathy using inductively coupled plasma emission spectroscopy. The presence of polyurethane was confirmed using CLRM in 2 of our cases. The decreased sensitivity of spectroscopy relative to routine histology may be due to the limited area of the lymph node sections that were evaluated using either CLRM or FITR spectroscopy-microspectroscopy. The spectroscopic evaluation was applied to multiple selected small areas in the lymph node sections. We have conducted limited studies using chemical imaging CLRM (Nnayakkara P, Centeno JA, and Katzin WE, manuscript in preparation). Based on our results, this method is more sensitive, as would be expected for a scanning technique. It is also likely that routine tissue processing removes a significant amount of silicone prior to embedding the tissue in paraffin.[41]

In addition to silicone gel-filled breast implants, there are other types of synthetic prostheses that are known to cause silicone lymphadenopathy. Christie et al[18] were the first to describe silicone lymphadenopathy in a patient with a silicone elastomer joint prostheses. Subsequent reports of this variant of silicone lymphadenopathy have included patients with implants involving metacarpophalangeal and interphalangeal joints of the hand,[1,4,8,22,27,36,43,44] metatarsophalangeal joints,[45,49] and the temporomandibular joint.[23] The predominant histologic finding, noted in each of the reported cases of silicone lymphadenopathy associated with silicone elastomer joint prostheses, is the presence of multinucleated giant cells that contain refractile, unstained material consistent with silicone. Abraham and Etz[1] also used laser-Raman microprobe to confirm the presence of silicone in an enlarged axillary lymph node from a patient with a silicone elastomer finger joint prosthesis. The absence of significant numbers of foamy macrophages in lymph nodes from patients with silicone elastomer prostheses suggests that this component of the response to silicone breast implants is likely related to the fact that breast implants contain a lower molecular weight and more fluid form of silicone.

There are a few reports of changes in lymph nodes related to nonsilicone prostheses. Gray et al[26] described 2 patients with lymphadenopathy related to large joint prostheses. They suggested that the changes represented a florid reaction to fragments of polyester or polyethylene. Bauer et al[6] described a patient with a knee prosthesis that used a carbon fiber-reinforced polyethylene tibial component, who had both carbon fibers and polyethylene particles in external iliac lymph nodes.

The mechanism whereby silicone escapes from the confines of a silastic shell and then migrates to lymph nodes is unclear. Once the implant shell is ruptured, silicone gel clearly gains access to the surrounding tissues; however, even in the absence of frank implant rupture, silicone gel can leak or "bleed" from an implant. Bleeding refers to the slow migration

of silicone gel through an intact implant shell and was described over 25 years ago.[5,7,63] The physical basis for so-called silicone gel bleed from a breast implant is uncertain. The rate of silicone gel bleed from intact implants has been estimated at up to 100 mg per year for older implants.[3] In one report, there was histologic evidence of silicone escape from an implant within only 12 days of the original implant insertion.[11] Once outside the implant, silicone is apparently able to migrate via lymphatic channels to gain access to regional lymph nodes. Evidence indicating migration of silicone from breast implants to various distant sites, including the upper extremity,[40] the groin,[14] the liver,[46] synovium,[55] skin,[55] and pleural fluid,[32] has also been reported. The presence of relatively large particles/droplets of silicone and polyurethane in regional lymph nodes of patients with breast implants suggests that the transit of various elements, either synthetic or biologic, from breast tissue to lymph nodes via lymphatic channels may have a significant passive component. This passive component may be an important factor in the metastatic process. Silicone and polyurethane migration from breast implants to lymph nodes may therefore represent a model that could be useful in understanding the passive component of metastasis in breast cancer. The process of migration of silicone and polyurethane to lymph nodes may also be similar to what has recently been described as "benign mechanical transport" of breast epithelial cells to sentinel lymph nodes.[21]

The clinical significance of silicone lymphadenopathy has several different facets. In a patient who has had postmastectomy reconstructive surgery using silicone gel breast implants, the clinical differential diagnosis of regional lymph node enlargement should include silicone lymphadenopathy as well as metastatic breast cancer. In most individuals with silicone gel breast implants, who have had surgery for breast augmentation, one must also consider the potential for adverse health consequences of silicone migration to regional lymph nodes. The relationship between silicone breast implants and systemic diseases is a highly controversial issue. In two well-publicized epidemiologic studies, the authors found no association between breast implants and a variety of specific, clinically defined connective-tissue diseases.[25,52] A meta-analysis of research on the relationship between autoimmune diseases and silicone breast implants[33] and an Institute of Medicine review[9] also concluded that there is no clear evidence that silicone breast implants cause systemic disease. In a commentary on the safety of breast implants, Zuckerman has pointed out limitations of both the meta-analysis and the Institute of Medicine review.[66] In their epidemiologic review, Silverman et al[56] concluded that information is insufficient to establish the overall health risks related to silicone breast implants. In addition, there are numerous reports of a wide variety of symptoms in women with breast implants, including myalgias, arthralgias, fatigue, memory disturbances, and sleep disorders.[10,20,24,59,64] Some authors argue that these symptoms may be related to silicone. Furthermore, Brown et al have recently found a statistically significant link between ruptured silicone gel implants and fibromyalgia as well as other connective-tissue diseases.[12,13] Kossovsky and Freiman have also reviewed much of the literature regarding the clinical and immunologic manifestations of silicone breast implants and has

proposed a model that seeks to explain the role of silicone in inciting rheumatologic disease.[37] The findings in our study do not specifically address the controversy regarding silicone gel implants and connective-tissue disease. Nevertheless, the possibility that silicone frequently migrates to regional lymph nodes of patients with silicone gel breast implants must be considered in assessing the safety of these medical devices. Although it is clearly not the intention of implant manufacturers to introduce silicone gel into lymph nodes, this phenomenon does provide a rational basis for suggesting that silicone gel implants may have an impact on the immune system. Finally, the role of silicone in the development of lymphoma at least deserves mention since there are several case reports describing primary breast lymphoma in patients with silicone gel breast implants as well as patients with coexistent silicone lymphadenopathy and lymphoma in the same lymph node.[4,19,43,50,51,64]

REFERENCES

1. Abraham JL, Etz ES. Molecular microanalysis of pathological specimens in situ with a laser-Raman microprobe. *Science*. 1979;206:716–718.
2. Ashley FL. A new type of breast prosthesis: preliminary report. *Plast Reconstr Surg*. 1970;45:421–424.
3. Baines CJ, Arseneau J, Davis P, et al. Summary of the report on silicone-gel-filled breast implants. *Can Med Assoc J*. 1992;147:1141–1146.
4. Benjamin E, Ahmed A, Rashid ATMF, et al. Silicone lymphadenopathy: A report of two cases, one with concomitant malignant lymphoma. *Diagn Histopathol*. 1982;5:133–141.
5. Barker DE, Retsky MI, Schultz S. Bleeding of silicone from bag-gel implants and its clinical relation to fibrous capsule reaction. *Plast Reconstr Surg*. 1978;61:836–841.
6. Bauer TW, Saltarelli M, McMahon JT, et al. Regional dissemination of wear debris from a total knee prosthesis. *J Bone Joint Surg Am*. 1993;75:106–111.
7. Bergman RB, van der Ende AE. Exudation of silicone through the envelope of gel-filled breast prostheses: an in vitro study. *Br J Plast Surg*. 1979;32:31–34.
8. Bernstein SA, Strickland RW, Lazarus E. Axillary lymphadenopathy due to Swanson implants. *J Rheumatol*. 1993;20:1066–1069.
9. Bondurant S, Ernster V, Herdman R, eds. *Safety of Silicone Breast Implants*. Washington, DC: Institute of Medicine, 1999.
10. Borenstein D. Siliconosis: a spectrum of illness. *Semin Arthritis Rheum*. 1994;24(suppl 1):1–7.
11. Brandt B, Breiting V, Christensen L, et al. Five years experience of breast augmentation using silicone gel prostheses with emphasis on capsule shrinkage. *Scand J Plast Reconstr Surg*. 1984;18:311–316.
12. Brown SL, Duggirala HJ, Pennello G. An association of silicone-gel breast implant rupture and fibromyalgia. *Curr Rheumatol Rep*. 2002;4:293–298.
13. Brown SL, Pennello G, Berg WA, et al. Silicone gel breast implant rupture, extracapsular silicone, and health status in a population of women. *J Rheumatol*. 2001;28:996–1003.
14. Capozzi A, DuBou R, Pennisi VR. Distant migration of silicone gel from a ruptured breast implant: case report. *Plast Reconstr Surg*. 1978;62:302–303.
15. Centeno JA, Johnson FB. Microscopic identification of silicone in human breast tissue by infrared microspectroscopy and x-ray microanalysis. *Appl Spectrosc*. 1993;47:341–345.
16. Centeno JA, Kalasinsky VF, Johnson FB, et al. Fourier transform infrared microscopic identification of foreign materials in tissue sections. *Lab Invest*. 1992;66:123–131.
17. Centeno JA, Mullick FG, Panos RG, et al. Laser-Raman microprobe identification of inclusions in capsules associated with silicone gel breast implants. *Mod Pathol*. 1999;12:714–721.
18. Christie AJ, Weinberger KA, Dietrich M. Silicone lymphadenopathy and synovitis: complications of silicone elastomer finger joint prostheses. *JAMA*. 1977;237:1463–1464.

19. Cook PD, Osborne BM, Connor RL, et al. Follicular lymphoma adjacent to foreign body granulomatous inflammation and fibrosis surrounding silicone breast prosthesis. *Am J Surg Pathol*. 1995;19:712–717.

20. Cuellar ML, Gluck O, Molina JF, et al. Silicone breast implant-associated musculoskeletal manifestations. *Clin Rheumatol*. 1995;14:667–672.

21. Diaz NM, Cox CE, Ebert M, et al. Benign mechanical transport of breast epithelial cells to sentinel lymph nodes. *Am J Surg Pathol*. 2004;28:1641–1645.

22. Digby JM, Wells AL. Malignant lymphoma with intranodal refractile particles after insertion of silicone prosthesis [Letter]. *Lancet*. 1981;ii:580.

23. Dolwick MF, Aufdemorte TB. Silicone-induced foreign body reaction and lymphadenopathy after temporomandibular joint arthroplasty. *Oral Surg Oral Med Oral Pathol*. 1985;59:449–452.

24. Freundlich B, Altman C, Snadorfi N, et al. A profile of symptomatic patients with silicone breast implants: a Sjögrens-like syndrome. *Semin Arthritis Rheum*. 1994;24(suppl 1):44–53.

25. Gabriel SE, O'Fallon WM, Kurland LT, et al. Risk of connective-tissue diseases and other disorders after breast implantation. *N Engl J Med*. 1994;330:1697–1702.

26. Gray MH, Talbert ML, Talbert WM, et al. Changes seen in lymph nodes draining the sites of large joint prostheses. *Am J Surg Pathol*. 1989;13:1050–1056.

27. Groff GD, Schned AR, Taylor TH. Silicone-induced adenopathy eight years after metacarpophalangeal arthroplasty. *Arthritis Rheum*. 1981;24:1578–1581.

28. Hardt NS, Yu LT, La Torre G, et al. Fourier transform infrared microspectroscopy used to identify foreign materials related to breast implants. *Mod Pathol*. 1994;7:669–676.

29. Hausner RJ, Schoen FJ, Pierson KK. Foreign-body reaction to silicone gel in axillary lymph nodes after an augmentation mammaplasty. *Plast Reconstr Surg*. 1978;62:381–384.

30. Hausner RJ, Schoen FJ, Mendez-Fernandez MA, et al. Migration of silicone gel to axillary lymph nodes after prosthetic mammoplasty. *Arch Pathol Lab Med*. 1981;105:371–372.

31. Hester TR, Nahai F, Bostwick J, et al. A 5-year experience with polyurethane-covered mammary prostheses for treatment of capsular contracture, primary augmentation mammaplasty, and breast reconstruction. *Clin Plast Surg*. 1988;15:569–585.

32. Hirmand H, Hoffman LA, Smith JP. Silicone migration to the pleural space associated with silicone-gel augmentation mammaplasty. *Ann Plast Surg*. 1994;32:645–647.

33. Janowsky EC, Kupper LL, Hulka BS. Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. *N Engl J Med*. 2000;342:781–790.

34. Kala SV, Lykissa ED, Lebovitz RM. Detection and characterization of poly(dimethylsiloxane)s in biological tissues by GC/AED and GC/MS. *Anal Chem*. 1997;69:1267–1272.

35. Kao CC, Rand RP, Holt CA, et al. Internal mammary silicone lymphadenopathy mimicking recurrent breast cancer. *Plast Reconstr Surg*. 1997;99:225–229.

36. Kircher T. Silicone lymphadenopathy: a complication of silicone elastomer finger joint prostheses. *Hum Pathol*. 1980;11:240–244.

37. Kossovsky N, Freiman CJ. Silicone breast implant pathology: clinical data and immunologic consequences. *Arch Pathol Lab Med*. 1994;118:686–693.

38. Kulber DA, Mackenzie D, Steiner JH, et al. Monitoring the axilla in patients with silicone gel implants. *Ann Plast Surg*. 1995;35:580–584.

39. Lin RP, DiLeonardo M, Jacoby RA. Silicone lymphadenopathy: a case report and review of the literature. *Am J Dermatopathol*. 1993;15:82–84.

40. Mason J, Apisarnthanarax P. Migratory silicone granuloma. *Arch Dermatol*. 1981;117:366–367.

41. McConnell JP, Moyer TP, Nixon DE, et al. Determination of silicon in breast and capsular tissue from patients with breast implants performed by inductively coupled plasma emission spectroscopy: comparison with tissue histology. *Am J Clin Pathol*. 1997;107:236–246.

42. Mikuz G, Hoinkes G, Propst A, et al. 'Silicone lymphadenopathia' following augmentation mammaplasty. *Chir Plast*. 1982;6:209–214.

43. Murakata LA, Rangwala AF. Silicone lymphadenopathy with concomitant malignant lymphoma. *J Rheumatol*. 1989;16:1480–1483.

44. Paplanus S, Payne CM. Axillary lymphadenopathy 17 years after digital silicone implants: study with x-ray microanalysis. *J Hand Surg Am*. 1988;13:411–412.

45. Péoc'h M, Duprez D, Grice G, et al. Silicone lymphadenopathy mimicking a lymphoma in a patient with a metatarsophalangeal joint prosthesis. *J Clin Pathol*. 2000;53:549–551.

46. Pfleiderer B, Garrido L. Migration and accumulation of silicone in the liver of women with silicone gel-filled breast implants. *Magn Reson Med*. 1995;33:8–17.

47. Raso DS, Greene WB, Vesely JJ, et al. Light microscopy techniques for the demonstration of silicone gel. *Arch Pathol Lab Med*. 1994;118:984–987.

48. Rivero MA, Schwartz DS, Mies C. Silicone lymphadenopathy involving intramammary lymph nodes: a new complication of silicone mammaplasty. *AJR Am J Roentgenol*. 1994;162:1089–1090.

49. Rogers LA, Longtine JA, Garnick MB, et al. Silicone lymphadenopathy in a long distance runner: complication of a silastic prosthesis. *Hum Pathol*. 1988;19:1237–1239.

50. Sahoo S, Rosen PP, Feddersen RM, et al. Anaplastic large cell lymphoma arising in a silicone breast implant capsule: a case report and review of the literature. *Arch Pathol Lab Med*. 2003;127:e115–e118.

51. Said JW, Tasaka T, Takeuchi S, et al. Primary effusion lymphoma in women: report of two cases of Kaposi's sarcoma herpes virus-associated effusion-based lymphoma in human immunodeficiency virus-negative women. *Blood*. 1996;88:3124–3148.

52. Sánchez-Guerrero J, Colditz GA, Karlson EW, et al. Silicone breast implants and the risk of connective-tissue diseases and symptoms. *N Engl J Med*. 1995;332:1666–1670.

53. Santos-Briz A Jr, López-Ríos F, Santos-Briz A, et al. Granulomatous reaction to silicone in axillary lymph nodes: a case report with cytologic findings. *Acta Cytol*. 1999;43:1163–1165.

54. Sever CE, Leith CP, Appenzeller J, et al. Kikuchi's histiocytic necrotizing lymphadenitis associated with ruptured silicone breast implant. *Arch Pathol Lab Med*. 1996;120:380–385.

55. Silver RM, Sahn EE, Allen JA, et al. Demonstration of silicon in sites of connective-tissue disease in patients with silicone-gel beast implants. *Arch Dermatol*. 1993;129:63–68.

56. Silverman BG, Brown SL, Bright RA, et al. Reported complications of silicone gel breast implants: an epidemiologic review. *Ann Intern Med*. 1996;124:744–756.

57. Sinclair TM, Kerrigan CL, Buntic R. Biodegradation of the polyurethane foam covering of breast implants. *Plast Reconstr Surg*. 1993;92:1003–1013.

58. Šmahel J. Tissue reactions to breast implants coated with polyurethane. *Plast Reconstr Surg*. 1978;61:80–85.

59. Solomon G. A clinical and laboratory profile of symptomatic women with silicone breast implants. *Semin Arthritis Rheum*. 1994;24(suppl 1):29–37.

60. Tabatowski K, Elson CE, Johnston WW. Silicone lymphadenopathy in a patient with a mammary prosthesis: fine needle aspiration cytology, histology and analytical electron microscopy. *Acta Cytol*. 1990;34:10–14.

61. Truong LD, Cartwright J, Goodman MD, et al. Silicone lymphadenopathy associated with augmentation mammaplasty. *Am J Surg Pathol*. 1988;12:484–491.

62. Vaamonde R, Cabrera JM, Vaamonde-Martín RJ, et al. Silicone granulomatous lymphadenopathy and siliconomas of the breast. *Histol Histopathol*. 1997;12:1003–1011.

63. van Diest PJ, Beekman WH, Hage JJ. Pathology of silicone leakage from breast implants. *J Clin Pathol*. 1998;51:493–497.

64. Vasey FB, Havice DL, Bocanegra TS, et al. Clinical findings in symptomatic women with silicone breast implants. *Semin Arthritis Rheum*. 1994;24(suppl 1):22–28.

65. Wintsch W, Šmahel J, Clodius L. Local and regional lymph node response to ruptured gel-filled mammary prostheses. *Br J Plast Surg*. 1978;31:349–352.

66. Zuckerman D. Commentary: are silicone implants safe? *Plast Surg Nurs*. 2002;22:63–65.