

# Anaplastic Large Cell Lymphoma Occurring in Women with Breast Implants: Analysis of 173 Cases

Garry S. Brody, M.D., M.Sc.  
Dennis Deapen, Dr.Ph.  
Clive R. Taylor, M.D.,  
D.Phil.

Lauren Pinter-Brown, M.D.  
Sarah Rose House-Lightner,  
B.A.

James S. Andersen, M.D.  
Grant Carlson, M.D.

Melissa G. Lechner, Ph.D.  
Alan L. Epstein, M.D.,  
Ph.D.

Los Angeles and Duarte, Calif.;  
Atlanta, Ga.; and Boston, Mass.

**Background:** The first silicone breast implant was inserted in 1962. In 1997, the first case of anaplastic large cell lymphoma (ALCL) in association with a silicone breast implant was reported. The authors reviewed 37 articles in the world literature reporting on 79 patients and collected another 94 unreported cases as of the date of submission.

**Methods:** The world literature was reviewed. Missing clinical and laboratory information was solicited from the authors and treating physicians. As several different specialties were involved, information was not in one place. Many (but not all) authors and treating physicians were responsive, resulting in incomplete data.

**Results:** ALCL lesions first presented as late peri-implant seromas, a mass attached to the capsule, tumor erosion through the skin, in a regional node, or discovered during revision surgery. The clinical course varied widely from a single positive cytology result followed by apparent spontaneous resolution, to disseminated treatment-resistant tumor and death. There was no preference for saline or silicone fill or for cosmetic or reconstructive indications. Where implant history was known, the patient had received at least one textured-surface device. Extracapsular dissemination occurred in 18 cases; nine of those were fatal. Histochemical markers were primarily CD-30<sup>+</sup> and Alk-1<sup>-</sup>. Other markers occurred at a lower frequency. Risk estimates ranged from one in 500,000 to one in 3 million women with implants.

**Conclusion:** Breast implant-associated ALCL is a novel manifestation of site- and material-specific lymphoma originating in a specific scar location, presenting a wide array of diverse characteristics and suggesting a multifactorial cause. (*Plast. Reconstr. Surg.* 135: 695, 2015.)

## PERTINENT IMPLANT HISTORICAL LANDMARKS

The first pair of silicone gel-filled implants were inserted in 1962 (published in 1963).<sup>1</sup> Their dimethylsiloxane shells were permeable to the lower molecular weight oils within the gel, which diffused through the envelope (bleed) into the breast parenchyma, axillary nodes, and surrounding tissue, producing multiple benign granulomas. Capsular contracture rates were very high. In 1983, a layer of diphenyl siloxane was sandwiched into the shell wall, and adding a more cohesive

gel produced an almost complete barrier to diffusion (Fig. 1, *above, left*). Contracture rates were lower with this design, but not eliminated. The

**Disclosure:** There was no personal funding for any of the authors other than to contract the services of Ms. House-Lightner from the Department of Preventive Medicine. Dr. Brody received no personal remuneration and was compensated only for travel expenses to meetings where he presented this work, including a five-city tour of Australia and New Zealand to inform the local plastic surgeons about ALCL at Allergan's invitation. The tissue culture work by Dr. Epstein was supported by Mentor Corp. (Santa Barbara, Calif.), Allergan, Inc. (San Diego, Calif.), and Cancer Therapeutics Laboratories, Inc. (Los Angeles, Calif.), of which Dr. Epstein and Dr. Taylor are cofounders. None of the other authors has received any personal remuneration or has any conflict of interest.

*From the Division of Plastic Surgery, Departments of Epidemiology and Pathology, Keck School of Medicine at the University of Southern California; the Division of Oncology and Hematology, David Geffen School of Medicine at the University of California, Los Angeles; the Division of Plastic Surgery, Emory University School of Medicine; City of Hope Cancer Hospital.*

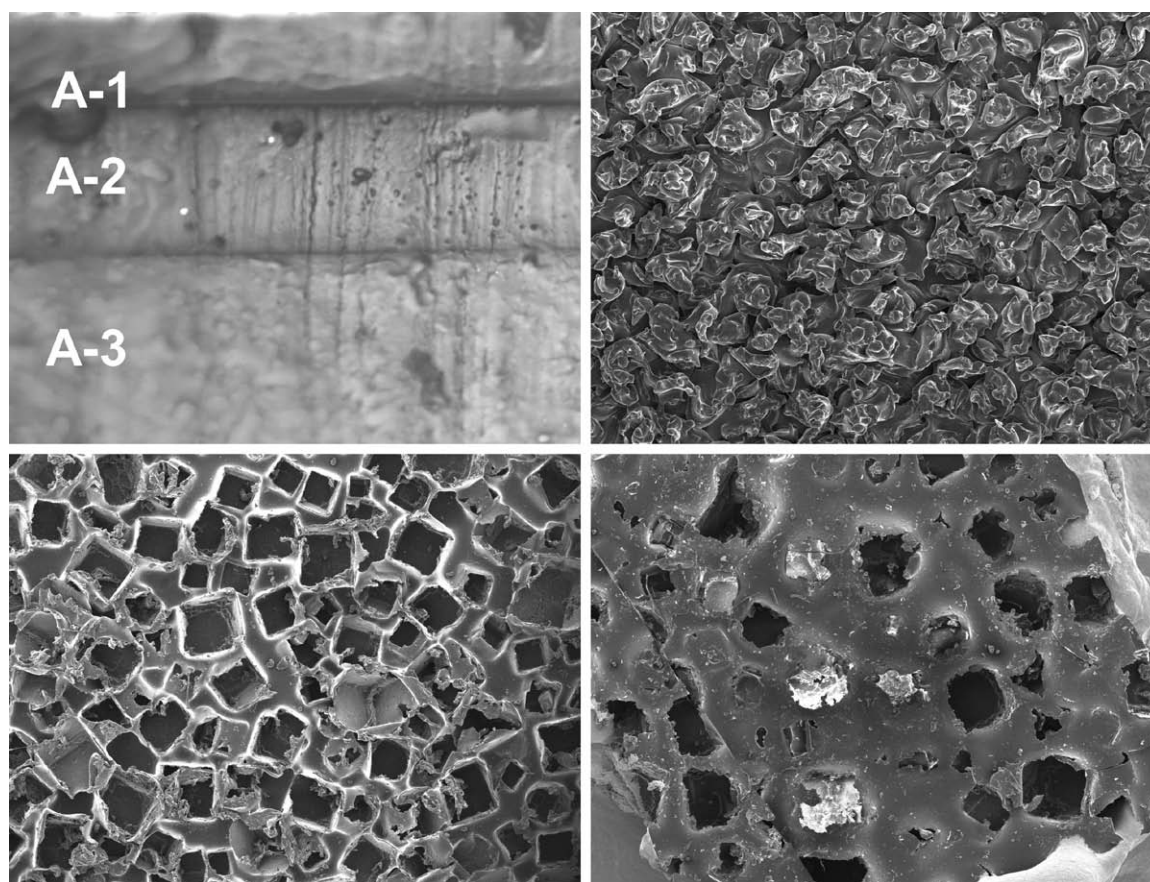
*Received for publication July 16, 2014; accepted August 28, 2014.*

*Copyright © 2014 by the American Society of Plastic Surgeons*

*DOI: 10.1097/PRS.0000000000001033*



This work was supported by  
THE PLASTIC SURGERY FOUNDATION.



**Fig. 1.** (Above, left) Scanning electron microscopic cross-section of smooth-surface implant (original magnification,  $\times 25$ ) (A-1, outer coat of dimethyl siloxane; A-2, central barrier layer of diphenyl siloxane; A-3, inner base of dimethyl siloxane). (Above, right) Electron microscopic photograph of Mentor textured shell surface (original magnification,  $\times 25$ ); averaging 40- to 100- $\mu\text{m}$ -high and 30- to 150- $\mu\text{m}$ -wide. (Below, left) Electron microscopic photograph shows unused Allergan textured shell surface (original magnification,  $\times 25$ ); averaging 600 to 800  $\mu\text{m}$  in diameter and 150 to 200  $\mu\text{m}$  in depth. (Below, right) Electron microscopic photograph of Allergan textured shell surface (original magnification,  $\times 25$ ), retrieved after explantation.

attempted solution, in 1987, was to mimic the apparent contracture resistance of one brand of polyurethane sponge-coated implants (discontinued in the United States in 1990, but still popular in other countries), by texturing the shell surface.

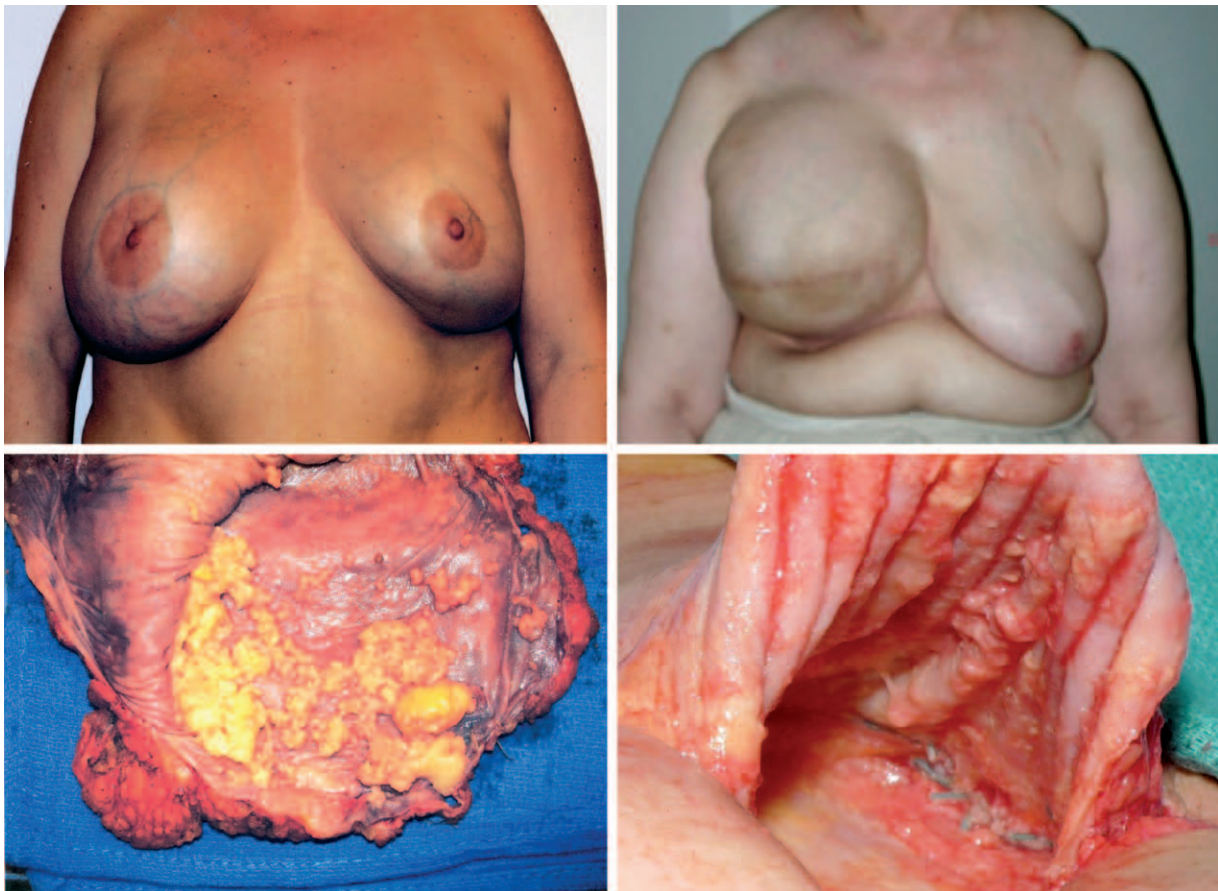
Currently, there are three major U.S. Food and Drug Administration–approved implant manufacturers marketing in the United States—Allergan (Allergan is used generically to include the Inamed, McGhan, and CUI companies, whom they acquired and whose texturing is the same or similar to Allergan’s), Mentor, and Sientra, each using different texturing processes. Allergan uses a “salt elution” process. The finished shell is dipped into liquid silicone, coated with salt crystals, redipped, and cured. The outer layer is then hand abraded to expose the salt, which is rinsed away. The resulting microscopic, fragile walled surface pits permit tissue ingrowth for attachment and rotational

stability (Fig. 1, *below, left*). Other manufacturers worldwide have patented variations of surface texturing processes generally designed for attachment. Removal of a well-attached Allergan device will leave embedded silicone surface particles in the capsule, disrupting the implant’s textured surface<sup>2</sup> (Fig. 1, *below, right*). Mentor Corp. uses a stamping technique, producing relatively thick, irregular pillars, a mirror image of the pits on the surface of polyurethane devices (Fig. 1, *above, right*). This design is thought to not integrate into the scar. However, two of the three Mentor cases in this study were reported to have silicone particles in the capsule. Sientra makes implants that use a proprietary gas expansion process; these implants were newly approved in 2012. The pits are finer and mostly do not firmly attach to the capsule.

### BREAST IMPLANTS AND ALCL

Primary lymphoma of the breast reportedly constitutes 0.4 to 0.5 percent of all breast malignancies, almost all of them of less aggressive B-cell origin.<sup>3</sup> A Surveillance, Epidemiology, and End Results query notes an incidence of primary breast anaplastic large cell lymphoma (ALCL) to be only three per 100 million per year in the United States, with a 75 percent mortality.<sup>4</sup> In 1997, Keech and Creech reported the first case of ALCL in a patient with a McGhan textured saline implant presenting initially as a 2-cm mass with diffuse involvement of the capsule. After total capsulectomy, the implant was replaced and followed by chemotherapy and radiation therapy. The patient was reportedly tumor-free 2 years later<sup>5</sup> (Fig. 2). Subsequently, small series and isolated case reports of ALCL arising in the implant capsule have appeared, often in the pathology and oncology literature.<sup>5–38</sup> Occasionally, the same patient was included in more than one report, as these series usually originated from referral centers where a few patients sought further care.

A population-based, nationwide pathology database in The Netherlands reported by de Jong et al.<sup>6</sup> identified five patients with breast ALCL who had cosmetic augmentation with textured silicone implants. Two were from Allergan and three were from European manufacturers using their own patented variations for surface texturing. A nested case control analysis was reported to have an estimated odds risk of implant-associated ALCL of 18.2 (95 percent CI, 2.1 to 156.8) (i.e., the odds of a woman with implants getting ALCL were 18.2 times that of controls). Surveillance, Epidemiology, and End Results program data, representing approximately 28 percent of the U.S. population, show between zero and 10 such cases annually from 2000 to 2011 out of well over 10 million women with breast implants, just in the United States. The U.S. Food and Drug Administration is quoted as stating that this “should not be of major concern to patients as the absolute risk remains very low due to the extreme rarity of breast ALCL.”<sup>38</sup>



**Fig. 2.** Gross appearance of a breast implant lymphoma-involved pocket. (Above, left) Seroma cosmetic augmentation. (Above, right) Seroma reconstructed breast. (Below, left) Débris laden implant capsule. (Below, right) Lymphoma-lined scar capsule.

## METHODS

Google, PubMed, Embase, and EBSCO were searched for newly reported cases. Most of the early literature was written from a pathology perspective, with limited details regarding the device and other clinical data. Acquisition of the full history was challenging, as multiple independent physicians were typically involved in the diagnosis and care, with one location rarely housing the entire patient record. Each corresponding author was contacted to direct us to other involved caregivers, who were then approached for further information and records. Some were unwilling or unable to respond, often citing institutional Health Insurance Portability and Accountability Act restrictions or difficulty locating older records. Many of the more recent cases were reported when first discovered immediately following completed workups.

Plastic surgeons, pathologists, and oncologists were alerted to the diagnosis at meeting presentations and journal articles, leading to the discovery of older unpublished cases and their device histories. Thus, the data were incomplete in some categories. The numbers reported in our results represent the most current totals known for each data point. Privacy was observed by the reporters with patient permissions or redacted identifiers. The anonymous patients' multiple records were collated and checked for duplication by matching age, location, and other clinical and pathologic information (Table 1). This study was granted a Health Insurance Portability and Accountability Act waiver.

## RESULTS

Thirty-seven reports from the world literature were reviewed,<sup>5–37</sup> documenting 79 cases. Another

94 cases were received from colleagues worldwide. In every case in this series, where the implant history was known, there was at least one textured device involved. Current estimates suggest that 20 to 40 of implant patients have had one or more revision operation for size change, malposition, rupture, contracture, or staged postmastectomy reconstruction.<sup>38–40</sup> The original implant may or may not have been replaced with a new one of the same or different design, fill, shell properties, and/or manufacturer and the capsule may or may not have been partially or totally removed. The tissue expanders used in postmastectomy reconstructions are usually similarly textured for rotational stability. When the expanders are replaced with a permanent implant, the capsules are not removed, often leaving embedded silicone particles behind (Fig. 1, *below, right*). Only 23 of the published reports from non-plastic surgeons documented the details of the implant itself, and they rarely described the implant history. The College of Pathologists has listed breast implants and tissue expanders on their “exempt from submission” list. Capsule tissue is not even mentioned.<sup>41</sup>

## Clinical Presentation and Outcomes

In addition to information from the published cases, we were able to obtain implant and expander histories for 127 of the cases from authors and colleagues. All but four of the 127 patients (three Mentor and one polyurethane) whose device history was known had at least one implant or tissue expander with the “lost salt” texturing or similar attachment process. Three patients had received both Allergan and Mentor implants, with the inciting device indeterminate. One case was from Sientra. Two unpublished reports of patients with

**Table 1. ALCL Demographics and Numerical Data (where known)**

Country	Company	Implant Fill	Presentation	Indication	Side
United States, 112	Allergan*, 97	Saline, 48	Seroma, 104	Cosmetic, 75	Left, 52
Australia, 20	Mentor, 3	Silicone, 61	Mass, 11	Reconstruction, 62	Right, 89
France, 9	Mentor and Allergan, 3	Polyurethane, 4	Seroma and mass, 11		Bilateral, 5
Canada, 5	Sientra, 1		Skin erosion, 3		Reconstruction, tumor side, 57
Holland, 5	PIP†, 5	Axillary nodes, 8			Reconstruction, opposite side, 5
Britain, 9	Nagor, 3	At surgery, 6			
Brazil, 4		Disseminated, 10			
New Zealand, 3					
Iran, 2					
Italy, 2					
Israel, 1					
Denmark, 1					

\*Allergan is used generically to include the McGhan and Cox companies, which were acquired by Allergan and whose texturing is the same or similar.

†The French-made implant PIP (Poly Implant Prothèse; also sold as Rofil) was illegally filled with industrial grade silicone and inserted in an estimated 300,000 or more women worldwide. The company is in bankruptcy and the owner has been jailed.

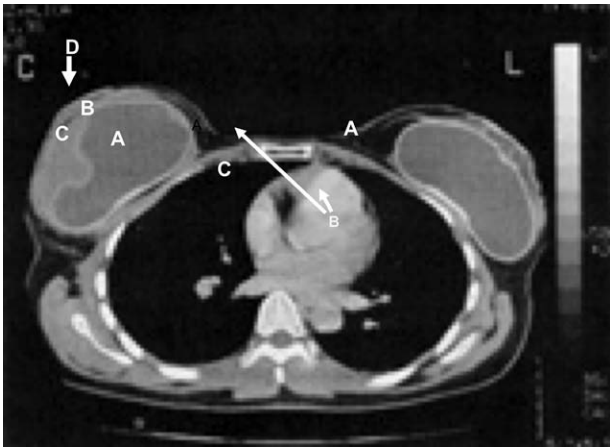
breast ALCL and only smooth implants were located. As in all of the other cases, the tumor arose in the capsule, and both of these patients' tumors presented within the breast parenchyma remote from the capsule without abnormality in the implant pocket; they may be presumed to be primary tumors in the breast, with questionable relationship to the implants.

No cases were identified before 1986, before surface-textured shells became available, but ALCL was not identified as an entity by the World Health Organization until 1985,<sup>42–44</sup> suggesting the possibility of some unrecognized cases before the textured era. However, there is no evidence to support this conjecture. Lipworth et al.<sup>45</sup> reviewed five long-term studies involving over 43,000 women with cosmetic implants spanning the time before and after onset of texturing and found no lymphomas of the breast. Deapen et al. reported on 3500 cosmetic patients all collected before 1981. A 37-year follow-up produced 11 lymphomas but none in the breast.<sup>46,47</sup>

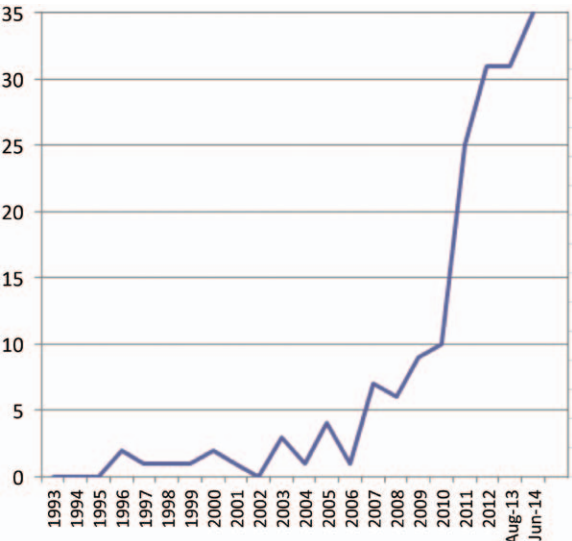
Unlike primary breast ALCL, these tumors arose from the implant scar capsule. The most common presenting sign was late onset (4 months to 25 years; median, 9.3 years after implantation) of a significant, often dramatic swelling of the breast from peri-implant fluid. Time from symptom onset to treatment ranged from 1 month to 2 years, with a surprising number of women not seeking care for many months (Fig. 3). Treatment delay did not appear to increase the risk of spread. Most patients reported that the swelling merely caused discomfort rather than true pain. Nine cases presented as a mass adherent to the scar envelope, all with at

least some associated fluid (Fig. 4, B), and six were found serendipitously during surgical revision for severe contracture. Three patients who underwent reconstruction presented with ulceration at the breast perimeter (Fig. 5). In three patients, the presenting symptom was a regional adenopathy, leading to discovery of ALCL in the capsule.

Technically, a lesion restricted to the capsule should be termed a "lymphoproliferative disorder." "Malignancy" should be reserved for metastatic lesions. Although these findings were generally true for most patients, there was an extremely broad spectrum of presentation and course, ranging from five women with just a few tumor cells in a single positive seroma aspirant and no further tumor found, to rapid onset in 10 women, with treatment resistance and rapid demise of nine



**Fig. 4.** Magnetic resonance imaging scan of ALCL-involved breast. (A) Implant shell and capsule. (B) Small seroma. (C) Palpable tumor. (Reproduced with permission from Keech, JA, Creech, BJ. Anaplastic T-cell lymphoma in proximity to a saline filled breast implant. *Plast Reconstr Surg.* 1997;100:554–555, with permission from Williams & Wilkins) (labels added).



**Fig. 3.** Number of newly diagnosed patients per year (where date is known) through June 1, 2014.



**Fig. 5.** Gross appearance of tumor eroding through the skin.

from disseminated disease.<sup>48</sup> The tenth patient was near death but rallied after treatment. She remains tumor-free at 2 years.<sup>10</sup> The patients with minimal involvement may represent a sampling error, as the lesion does not always involve the entire envelope and/or may be sparse in the fluid. Tumor cells were usually found in both the fluid and the capsule but occasionally were seen in only one or the other. In every case where the complete implant history was known, the patient had received at least one textured surface device. Three patients had a history of sprue,<sup>9,35</sup> which has a known modest increased risk for lymphoma—usually abdominal (marginal zone lymphoma, mucosa-associated lymphoid tissue-type) and three had been treated previously for Hodgkin lymphoma. None of these six patients' tumors spread beyond the capsule. Usually, the initial impression from frozen section was carcinoma, with the definitive diagnosis revealed following histochemical analysis.

The fluid associated with ALCL tended to be cloudy and debris filled, or varying from clear amber to a white or yellowish creamy fluid, often initially mistaken for infection (Fig. 4). Routine cultures were always negative; however, no attempts had been made in these cases to evaluate for biofilm organisms. B symptoms (night sweats, fatigue, and weight loss) were reported in only five of the 10 patients with disseminated disease. Lesions were confined to the capsule in 155 patients, and eight patients had local metastases, axillary and/or mediastinal. One patient presented with a seventh nerve palsy from an intracranial lesion.<sup>6</sup> Those who died all initially presented with full-blown disseminated disease, including enlarged fluid- and/or debris-filled capsules. Our data do not confirm the speculation of several authors that cases presenting as palpable tumors were necessarily more aggressive, as only four of the patients who died presented with a mass. Note that the original case described by Keech and Creech presented with a mass, but her outcome was positive,<sup>5</sup> and the cases presenting as adenopathy had no breast symptoms.

In three cases where the tumor was excised incompletely and no therapy was given, there have been no known recurrences to date; however, two have been lost to follow-up, which may possibly represent spontaneous regression. Recurrence was reported to have occurred in another three patients, but it is not known whether the capsule was excised completely.<sup>7</sup> Only three patients demonstrated invasion of the breast parenchyma itself.<sup>7</sup> Interestingly, associated cutaneous lymphoid papuloses (Fig. 6), large cell lymphoma involving the ipsilateral chest and breast skin, were seen in



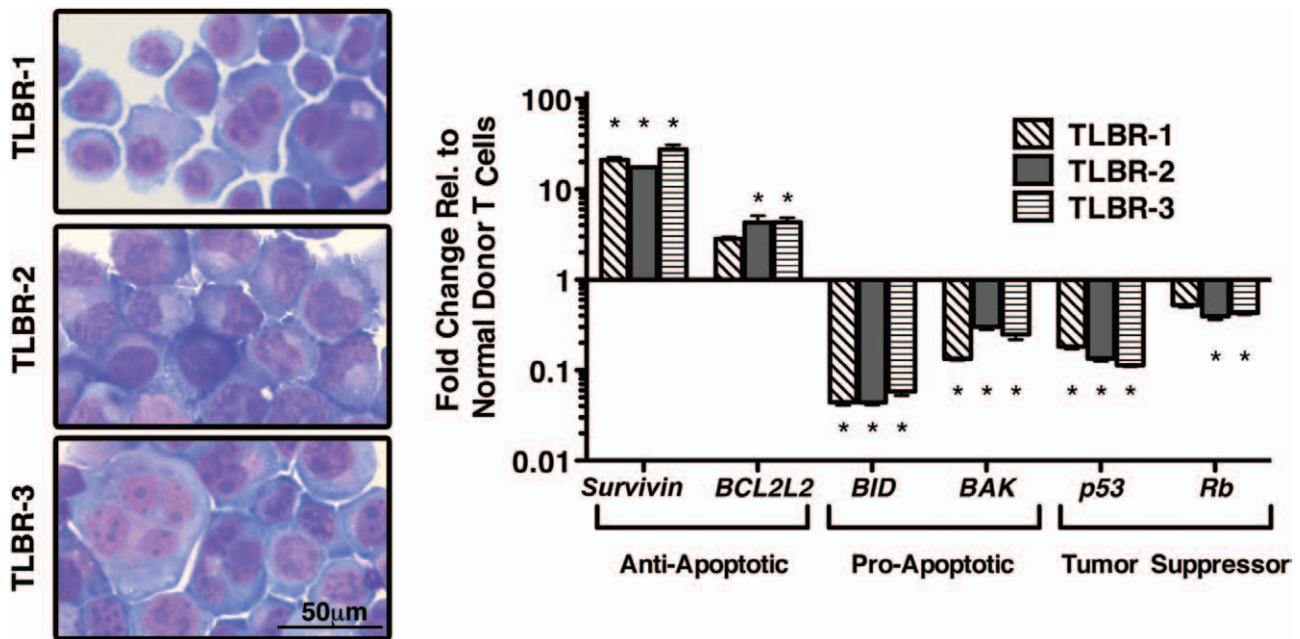
**Fig. 6.** Lymphomatoid papulosis of the breast. Photograph courtesy Dr. Marshal Kadin. Not associated with a breast implant but presented for information only.

five patients (Fig. 7). The aggressive microscopic appearance of the cells and similar immunophenotype and cytokine profile, the mostly benign clinical course of both ALCL and cutaneous T-cell lymphoma, and the cellular similarities suggest a relationship and speculation toward a possible genetic predisposition.<sup>49–52</sup>

Formerly, cases in which the tumor was restricted to the capsule received full courses of chemotherapy and/or radiotherapy. As the indolent nature of the lesions restricted to the capsule became apparent, most oncologists are now recommending only close follow-up for this group after total capsulectomy, reserving further therapy for possible recurrence.<sup>51</sup> All of the patients with only regional dissemination responded to oncologic therapy. Those who died as a result of disseminated disease had rapid downhill courses despite all therapeutic attempts.

### Pathology and Cell Culture

Thirty-six specimens submitted from colleagues were reexamined to confirm reported immunohistochemical results (ALK-1<sup>-</sup> and CD30<sup>+</sup>). Other T-cell markers occurred at a lower frequency. B-cell markers (CD20, CCD79a, and PAX5) were performed in a few cases, and all were reported as negative. Of the 13 specimens in which T-cell gene rearrangement studies were performed, 12 were reported as positive for monoclonality. B-cell (immunoglobulin H) rearrangements were also seen in the samples of four cases that were shown to be clonal in origin. In our samples, silicone particles were sparsely seen in only four of 11 samples. As sampling is necessarily random, if there is no obvious lesion, the biopsy specimen may have come from an area of nonattachment of the implant.<sup>53</sup>



**Fig. 7.** T-cell breast lymphoma (TLBR) cell lines as models for breast implant-associated ALCL. (Left) Wright-Giemsa staining of cytopsin specimens of the TLBR-1, -2, and -3 cell lines demonstrates large anaplastic cells with prominent nucleoli, abundant cytoplasm with prominent Golgi zones, and multinucleated giant cells (original magnification,  $\times 400$ ). (Right) Gene expression of the TLBR cell lines compared with normal donor T cells for apoptosis regulating and tumor suppressor genes as determined by quantitative reverse-transcriptase polymerase chain reaction. Mean fold change in gene expression is shown with standard error of the mean ( $*p < 0.05$ ).

Four fresh tissue samples provided by colleagues were cultured successfully, thus establishing T-cell breast lymphoma (TLBR) cell culture lines (TLBR-1 to TLBR-3). Characterization of the TLBR cell lines showed them to be interleukin-2 dependent; have high expression of CD30, survivin, and Notch 1; and to be monoclonal in origin with nearly triploid karyotypes (Fig. 7). Inhibitors of Notch1, survivin, and other transduction signals showed increased expression in these lymphomas. These TLBR cell lines will facilitate the testing of new therapies, including the use of anti-CD30 antibody therapy now approved for Hodgkin disease<sup>54,55</sup> (Fig. 5).

STAT3 is a transcription factor and oncogene with a critical role in cell proliferation. A mutated version is characteristically seen in strongly CD30<sup>+</sup> and ALK<sup>-</sup> lymphoproliferative disorders of the skin and other T-cell lymphomas. It was expressed in all four ALCL cultured tissue samples.<sup>56</sup>

Hu et al.,<sup>59</sup> in a preliminary study, found a variety of biofilm organisms including Gram negative bacteria with an increase in T-cell response in both humans and implanted pigs. They speculate that these findings “may point to an as yet unproven causative association between chronic bacterial biofilm infection and the genesis of this rare malignancy.” As biofilm has been ubiquitous from the beginning of breast implantation this would

be, at best, one of the components of a multifactorial etiology.<sup>57</sup>

### Demographics

The demographics are also unusual. Currently, there are only two Asians, one Native American, but no known cases in African American women. Implants are as popular or possibly more so in China, Europe, and Brazil, yet only 26 cases were found in the Eurozone, with a larger population than the United States, despite the awareness generated by the recent implant scandal in France (Table 1). Sweden, Finland, and Denmark have excellent implant registries, with Denmark only recently reporting one case.<sup>59,60</sup> This may represent a lack of awareness or reporting, which is seemingly unlikely, as the characteristics of this entity have been widely publicized in meetings in the Western world and in the plastic surgery, pathology, and oncology literature internationally. Both France and Britain have also established lymphoma registries. Counterintuitively, manufacturers estimate that 70 to 80 percent of implants sold in North America are smooth, whereas 70 to 80 percent sold in Europe are textured.<sup>61</sup>

### DISCUSSION

The rarity of this lesion precludes confirmation of cause with statistical certainty and suggests

a multifactorial inflammatory cause. Although many of the patient data are incomplete, we believe there is enough information to characterize this tumor and theorize certain etiologic considerations. No cases were located from the early pre-textured implant era, even where volumes of silicone gel migrated into the breast parenchyma, surrounding tissues, and regional nodes, producing multiple granulomas. None were found in patients with documented smooth devices only. These observations suggest a probable chronic inflammatory cause. Implant capsules are rich in Th17 T cells,<sup>61</sup> which are associated with inflammation as part of the cellular immune system. They are abundant in the implant capsule, more so in textured than in smooth,<sup>62</sup> and are similarly present in cutaneous T-cell lymphoma. This supports the hypothesis that breast implant-associated ALCL is related to cutaneous ALCL with respect to behavior, morphology, immunophenotype, and cytokine profile as speculated by Kadin et al.<sup>50</sup>

Paradoxically, in contrast to this conjecture of the rough surface as a cause in the breast capsule, Oppenheimer<sup>64</sup> found that smooth surfaced foreign bodies implanted in animals were sarcogenic, whereas rough or irregular surfaces did not generate tumors (Oppenheimer effect). There is an extensive literature confirming Oppenheimer's finding in laboratory animals, raising questions about the relevance of animal experiments for this lesion.<sup>65,66</sup>

When silicone wrist bone, finger, and toe joint prosthetic replacements are abraded against rough bone edges, they particulate, producing a florid local synovitis. Particles may occasionally migrate to the axillary nodes, resulting in an inflammatory lymphadenopathy. There are three reports of nodal lymphomas, all B-cell varieties, treated by adenectomy and therapy.<sup>67,68</sup> Other foreign body-related chronic inflammation-associated lymphoma reports were all the less aggressive B-cell lesions.

Sarcomas are the most common malignancies associated with orthopedic<sup>68</sup> materials, similarly attributed to abrasion debris from metal or polyethylene wear particulation. Softer materials such as mesh generally stimulate the less malignant B-cell lymphomas.<sup>69–71</sup> The specificity of this tumor's unique occurrence exclusively in the breast capsule, the implant surface characteristics, the unusual demographics, and the few associated ipsilateral cutaneous T-cell lymphoma lesions suggest a site-specific, material-specific, multifactorial cause initiated by textured surface silicone implants. This also supports speculation

of a possible genetic predisposition as suggested for cutaneous T-cell lymphoma. One exception is a literature report of an implant-associated non-breast T-cell tumor, surprisingly, in the scar overlying a tibial orthopedic plate.<sup>72</sup>

## CONCLUSIONS

Implant-associated ALCL appears to be a new, distinct entity with a multifactorial cause and the first known presentation of large cell lymphoma arising in scar tissue. This report is a collation of the currently known spectrum of this extremely rare disorder with an attempt to fashion a cohesive etiologic theory from the disparate available information about its multiple unique properties and behavior. The clinical presentation varies widely, from benign characteristics of an indolent lymphoproliferative disorder to a fulminant, malignant, treatment-resistant demise. The common factors appear to be the texturing of the silicone breast implant surface, suggesting a site- and material-specific chronic inflammatory cause, and the demographics, associated skin lesions, and tissue culture results suggesting a possible rare genetic predisposition. Biofilm organisms may also play a role. It appears to be unrelated to the implant fill material or cosmetic versus reconstructive indications. What remains to be resolved is why a presumed etiologic factor of chronic irritation or inflammation in the breast implant milieu results in ALCL, whereas elsewhere it is manifested by the less aggressive B lesions. For most patients, the disease is limited to the scar envelope, a lymphoproliferative lesion with a much more indolent course than the cellular morphology would suggest. The tumor is not time dependent in that it can arise within months or up to 25 years after implantation, and delay from first symptoms to treatment in most patients does not seem to alter the course of the disease. A careful staging evaluation should dictate the appropriate treatment plan. Although the fluid and scar capsule usually appear abnormal, they can seem grossly normal and therefore it is recommended that all fluid and capsule tissue from patients with seromas should be submitted for analysis. Recently, it has been suggested that if the tumor is restricted to the capsule, only bilateral implant removal with total capsulectomies should be considered with close follow-up, and without oncologic treatment. Multiagent chemotherapy (cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone) with or without radiation has been successful for local extracapsular involvement, but even high-dose stem cell infusion

by means of marrow transplantation in patients with aggressive disseminated disease was successful in only one of the 10 patients. Finally, we hope that the College of Pathologists would consider removing breast implants and tissue expanders from their exempt from submission list and document the manufacturer, size, fill, surface characteristic, and batch number as noted on most devices.

Garry S. Brody, M.D., M.Sc.  
Division of Plastic Surgery  
Keck School of Medicine  
University of Southern California  
1510 San Pablo St., #415  
Los Angeles, Calif. 90033  
gsbmd@aol.com

### ACKNOWLEDGMENTS

*This study was funded by a grant from The Plastic Surgery Foundation of the American Society of Plastic Surgeons. The authors wish to acknowledge and thank all of the many physicians, office personnel, patients, and patient's relatives who generously shared their information with us. They also thank their colleagues who provided the clinical photographs and tissue samples; the authors regret that public identification of these colleagues might risk a Health Insurance Portability and Accountability Act violation. They would especially like to acknowledge the participation of Drs. S. E. Martin and W. Elatra who assisted in the early phases of this research.*

### DISCLAIMER

*All conclusions identified as tentative, speculative, or suggestive represent the personal analysis of the first author (G.S.B.).*

### REFERENCES

- Cronin TD, Gerow FJ. Augmentation mammoplasty: A new "natural feel" prosthesis. In: *Transactions of the Third International Congress of Plastic Surgery*. Amsterdam: Excerpta Medica Foundation; 1963:41–49.
- Lesesne CB. Textured surface silicone breast implants: Histology in the human. *Aesthetic Plast Surg*. 1997;21:93–96.
- Jeanneret-Sozzi W, Taghian A, Epelbaum R, et al. Primary breast lymphoma: Patient profile, outcome and prognostic factors. A multicentre Rare Cancer Network study. *BMC Cancer* 2008;8:86.
- Altekruse SF, Kosary CL, Krapcho M, et al. *SEER Cancer Statistics Review, 1975–2007*. Bethesda, Md: National Cancer Institute; 2010. Available at: [http://seer.cancer.gov/csr/1975\\_2007/](http://seer.cancer.gov/csr/1975_2007/). Accessed January 27, 2015.
- Keech JA Jr, Creech BJ. Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant. *Plast Reconstr Surg*. 1997;100:554–555.
- de Jong D, Vasmel WL, de Boer JP, et al. Anaplastic large-cell lymphoma in women with breast implants. *JAMA* 2008;300:2030–2035.
- Aladily TN, Medeiros JL, Amin MB, et al. Anaplastic large cell lymphoma associated with breast implants: A report of 13 cases. *Am J Surg Pathol*. 2012;36:1000–1008.
- Popplewell L, Thomas SH, Huang Q, Chang KL, Forman SJ. Primary anaplastic large-cell lymphoma associated with breast implants. *Leuk Lymphoma* 2011;52:1481–1487.
- Gaudet G, Friedberg JW, Weng A, Pinkus GS, Freedman AS. Breast lymphoma associated with breast implants: Two case-reports and a review of the literature. *Leuk Lymphoma* 2002;43:115–119.
- Taylor KO, Webster HR, Prince HM. Anaplastic large cell lymphoma and breast implants: Five Australian cases. *Plast Reconstr Surg*. 2012;129:610e–617e.
- Roden AC, Macon WR, Keeney GL, Myers JL, Feldman AL, Dogan A. Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: An indolent T-cell lymphoproliferative disorder. *Mod Pathol*. 2008;21:455–463.
- Sahoo S, Rosen PP, Feddersen RM, Viswanatha DS, Clark DA, Chadburn A. 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.
- Smith TJ, Ramsaroop R. Breast implant related anaplastic large cell lymphoma presenting as late onset peri-implant effusion. *Breast* 2012;21:102–104.
- Mora P, Melo AC, Amorim GLS, Scheliga AA. Primary T-cell anaplastic lymphoma associated to a breast implant: Case report. *Haematologica* 2009;94:658–659.
- Neuman MK, Zimmel NJ, Bandak AZ, Kaplan BJ. Primary breast lymphoma in a patient with silicone breast implants: A case report and review of the literature. *J Plast Reconstr Aesthet Surg*. 2007;61:822–825.
- Gualco G, Chioato L, Harrington WJ Jr, Weiss LM, Bacchi CE. Primary and secondary T-cell lymphomas of the breast: Clinico-pathologic features of 11 cases. *Appl Immunohistochem Mol Morphol*. 2009;17:301–306.
- Do V, Shifrin DA, Oostendorp L. Lymphoma of the breast capsule in a silicone implant-reconstructed patient. *Am Surg*. 2010;76:1030–1031.
- Bishara MR, Ross C, Sur M. Primary anaplastic large cell lymphoma of the breast arising in reconstruction mammoplasty capsule of saline filled breast implant after radical mastectomy for breast cancer: An unusual case presentation. *Diagn Pathol*. 2009;4:11.
- Wong AK, Lopategui J, Clancy S, Kulber D, Bose S. Anaplastic large cell lymphoma associated with a breast implant capsule: A case report and review of the literature. *Am J Surg Pathol*. 2008;32:1265–1268.
- Alobeid B, Sevilla DW, El-Tamer MB, Murty VV, Savage DG, Bhagat G. Aggressive presentation of breast implant-associated ALK-1 negative anaplastic large cell lymphoma with bilateral axillary lymph node involvement. *Leuk Lymphoma* 2009;50:831–833.
- Olack B, Gupta R, Brooks GS. Anaplastic large cell lymphoma arising in a saline breast implant capsule after tissue expander breast reconstruction. *Ann Plast Surg*. 2007;59:56–57.
- Hanson SE, Gutowski KA. Primary T-cell lymphoma associated with breast implant capsule. *Plast Reconstr Surg*. 2010;126:39e–41e.
- Kumar SR, Sanaei O, Vasef M, Rabinowitz I, Fekrazad MH. Anaplastic large cell lymphoma associated with breast implants. *World J Plast Surg*. 2012;1:30–35.
- Rajabiani A, Arab H, Emami A, Manafi A, Bazzaz N, Saffar H. Anaplastic large cell lymphoma associated with breast implant: A case report. *World J Plast Surg*. 2012;1:46–50.
- George EV, Pharm J, Houston C, et al. Breast implant associated ALK-negative anaplastic large cell lymphoma: A case

- report and discussion of possible pathogenesis. *Int J Clin Exp Pathol*. 2013;6:1632–1642.
26. Ivaldi C, Perchenet AS, Jallut Y, Casanova D. Two cases of lymphoma in an implant capsule: A difficult diagnosis, an unknown pathology (in French). *Ann Chir Plast Esthet*. 2013;58:688–693.
  27. Talagas M, Uguen A, Charles-Petillon F, et al. Breast implant-associated anaplastic large-cell lymphoma can be a diagnostic challenge for pathologists. *Acta Cytol*. 2014;58:103–107.
  28. Lee M, Cooper B, Becker D. Keeping abreast of axillary masses. *Lancet*. 2012;380:1530.
  29. Lazzeri D, Agostini T, Giannotti G, et al. Null type anaplastic lymphoma, kinase-negative anaplastic large cell lymphoma arising in a silicone breast implant capsule. *Plast Reconstr Surg*. 2011;127:159e–162e.
  30. Mies C, Goyal A, Begg A, et al. Breast implant capsule anaplastic large cell lymphoma (BIC-ALCL). *Int J Clin Exp Pathol*. 2013;6:1631–1642.
  31. Farace F, Bulla A, Marongiu F, et al. Anaplastic large cell lymphoma of the breast arising around mammary implant capsule: An Italian report. *Aesthetic Plast Surg*. 2013;37:567–571.
  32. Fritzsche FR, Pahl S, Petersen I, et al. Anaplastic large-cell non-Hodgkin's lymphoma of the breast in periprosthetic localisation 32 years after treatment for primary breast cancer: A case report. *Virchows Arch*. 2006;449:561–564.
  33. Li S, Lee AK. Silicone implant and primary breast ALK1-negative anaplastic large cell lymphoma, fact or fiction? *Int J Clin Exp Pathol*. 2010;3:117–121.
  34. Sørensen K, Murphy J, Lennard A, Wadehra V, Menon GK, Collis N. Anaplastic large cell lymphoma in a reconstructed breast using a silicone implant: A UK case report. *J Plast Reconstr Aesthet Surg*. 2014;67:561–563.
  35. Zakhary JM, Hamidian Jahromi A, Chaudhery S, Kim M. Anaplastic large cell lymphoma in the setting of textured breast implant: A call for patients and physicians education. *J La State Med Soc*. 2013;165:26–29.
  36. Hart AM, Lechowicz MJ, Peters KK, Holden J, Carlson GW. Breast implant-associated anaplastic large-cell lymphoma: Two case reports and review of the literature. *ASJ*. 2014;34:884–894.
  37. De Silva IM, Teague JA, Blake WE. Breast implant associated anaplastic large cell lymphoma: A case report and reconstructive option. *J Plast Reconstr Aesthet Surg*. 2013;66:1773–1776.
  38. The Center for Devices and Radiological Health, U.S. Food and Drug Administration. Anaplastic large cell lymphoma (ALCL) in women with breast implants: Preliminary FDA findings and analysis. Available at: <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/UCM240003.pdf>.
  39. Allergan, Inc. Safety and effectiveness of Natrelle cohesive round silicone-filled breast implants. Available at: <http://clinicaltrials.gov/ct2/show/NCT00689871>.
  40. Allergan, Inc. Safety and effectiveness of Style 410 silicone-filled breast implant study. Available at: <http://clinicaltrials.gov/ct2/show/NCT00690339>.
  41. College C, Feigal R, Wandera A, Strange M. Bilateral versus unilateral mandibular block anesthesia in a pediatric population. *Pediatr Dent*. 2000;22:453–457.
  42. Stein H, Foss HD, Dürkop H, et al. CD30(+) anaplastic large cell lymphoma: A review of its histopathologic, genetic, and clinical features. *Blood*. 2000;96:3681–3695.
  43. Jaffe ES. Anaplastic large cell lymphoma: The shifting sands of diagnostic hematopathology. *Mod Pathol*. 2001;14:219–228.
  44. Kinney MC, Higgins RA, Medina EA. Anaplastic large cell lymphoma: Twenty-five years of discovery. *Arch Pathol Lab Med*. 2011;135:19–43.
  45. Lipworth L, Tarone RE, McLaughlin JK. Breast implants and lymphoma risk: A review of the epidemiologic evidence through 2008. *Plast Reconstr Surg*. 2009;123:790–793.
  46. Deapen DM, Pike MC, Casagrande JT, Brody GS. The relationship between breast cancer and augmentation mammoplasty: An epidemiologic study. *Plast Reconstr Surg*. 1986;77:361–368.
  47. Deapen DM, Brody GS. Cancer risk among cosmetic breast implant patients: An update of the Los Angeles study. *Plast Reconstr Surg*. 2012;129:575e–576e.
  48. Carty MJ, Pribaz JJ, Antin JH, et al. A patient death attributable to implant-related primary anaplastic large cell lymphoma of the breast. *Plast Reconstr Surg*. 2011;128:112e–118e.
  49. Kadin M, Xu H, Pavlov I, et al. Breast implant associated ALCL closely resembles primary cutaneous ALCL. *Lab Invest*. 2012;92(Suppl 1):346A.
  50. Kim B, Roth C, Chung KC. Anaplastic large cell lymphoma and breast implants: A systematic review. *Plast Reconstr Surg*. 2011;127:2141–2150.
  51. Chott A, Vonderheid EC, Olbricht S, Miao NN, Balk SP, Kadin ME. The dominant T cell clone is present in multiple regressing skin lesions and associated T cell lymphomas of patients with lymphomatoid papulosis. *J Invest Dermatol*. 1996;106:696–700.
  52. Wang HH, Myers T, Lach LJ, Hsieh CC, Kadin ME. Increased risk of lymphoid and nonlymphoid malignancies in patients with lymphomatoid papulosis. *Cancer*. 1999;86:1240–1245.
  53. Pinter-Brown LC. Discussion: A patient death attributable to implant-related primary anaplastic large cell lymphoma of the breast. *Plast Reconstr Surg*. 2011;128:122e–123e.
  54. Taylor CR, Siddiqi IN, Brody GS. Anaplastic large cell lymphoma occurring in association with breast implants: Review of pathologic and immunohistochemical features in 103 cases. *Appl Immunohistochem Mol Morphol*. 2013;21:13–20.
  55. Lechner ML, Megial C, Church CH, et al. Survival signals and targets for therapy in breast implant-associated ALK-anaplastic large cell lymphoma. *Clin Cancer Res*. 2012;18:4549–4559.
  56. Lechner MG, Lade S, Liebertz DJ, et al. Breast implant-associated ALK-negative T cell anaplastic large-cell lymphoma: Establishment and characterization of a model cell line (TLBR-1) for this newly emerging clinical entity. *Cancer*. 2011;117:1478–1489.
  57. Ohgami RS, Ma L, Merker JD, Martinez B, Zehnder JD, Arber DA. STAT3 mutations are frequent in CD30+ T-cell lymphomas and T-cell large granular lymphocytic leukemia. *Leukemia*. 2013;27:2242–2247.
  58. Hu H, Jacombs A, Vickery K, Merten SL, Pennington DG, Deva AK. Chronic biofilm infection in breast implants is associated with an increased T cell lymphocytic infiltrate - implications for breast implant associated lymphoma. *Plast Reconstr Surg*. November 7, 2014; doi: 10.1097/PRS.0000000000000886 [Epub ahead of print].
  59. McLaughlin JK, Lipworth L, Fryzek JP, Ye W, Tarone RE, Nyren O. Long-term cancer risk among Swedish women with cosmetic breast implants: An update of a nationwide study. *J Natl Cancer Inst*. 2006;98:557–560.
  60. Pukkala E, Boice JD Jr, Hovi SL, et al. Incidence of breast and other cancers among Finnish women with cosmetic breast implants, 1970-1999. *J Long Term Eff Med Implants*. 2002;12:271–279.
  61. J. Canady, Mentor Corporation, personal communication.
  62. Wolfram D, Rabensteiner E, Grundtman C, et al. T-regulatory cells and TH17 cells in peri-silicone implant capsular fibrosis. *Plast Reconstr Surg*. 2012;129:327e–337e.

63. Meza Britez ME, Caballero Llana C, Chaux A. Periprosthetic breast capsules and immunophenotypes of inflammatory cells. *Eur J Plast Surg*. 2012;35:647–651.
64. Oppenheimer ET, Willhite M, Danishefsky I, Stout AP. Observations on the effects of powdered polymer in the carcinogenic process. *Cancer Res*. 1961;21:132–134.
65. James SJ, Pogribna M, Miller BJ, Bolon B, Muskhelishvili L. Characterization of cellular response to silicone implants in rats: Implications for foreign-body carcinogenesis. *Biomaterials* 1997;18:667–675.
66. Kirkpatrick CJ, Alves A, Köhler H, et al. Biomaterial-induced sarcoma: A novel model to study preneoplastic change. *Am J Pathol*. 2000;156:1455–1467.
67. Murakata LA, Rangwala AF. Silicone lymphadenopathy with concomitant malignant lymphoma. *J Rheumatol*. 1989;16:1480–1483.
68. Digby JM. Malignant lymphoma with intranodal silicone rubber particles following metacarpophalangeal joint replacements. *Hand* 1982;14:326–332.
69. Keel SB, Jaffe KA, Petur Nielsen G, Rosenberg AE. Orthopaedic implant-related sarcoma: A study of twelve cases. *Mod Pathol*. 2001;14:969–977.
70. Moizhess TJ. Carcinogenesis induced by foreign bodies. *Biochemistry (Mosc.)* 2008;73:763–775.
71. Loong F, Chan AC, Ho BC, et al. Diffuse large B-cell lymphoma associated with chronic inflammation as an incidental finding and new clinical scenarios. *Mod Pathol*. 2010;23:493–501.
72. Bharath P, Paturi A, Stone RG, et al. Soft tissue anaplastic large T-cell lymphoma associated with a metallic orthopedic implant: Case report and review of the current literature. *J Foot Ankle Surg*. 2010;49:561–564.

