Anaplastic Large T-Cell Lymphoma and Breast Implants: A Review of the Literature

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Background: Anecdotal reports and one case-control study suggested an association, without evidence of causation, between breast implants and anaplastic lymphoma kinase–negative anaplastic large T-cell lymphoma (ALCL), a rare non-Hodgkin's lymphoma. This review summarizes the published evidence, including case reports and epidemiologic studies.
Methods: A PubMed search limited to English language articles was conducted using the search terms "breast implant" and "lymphoma," "primary T-cell breast lymphoma," or "breast implant and ALCL" to identify all published cases of breast-associated ALCL.
Results: A total of 18 publications were retrieved describing 27 cases of ALCL in breast implant recipients. Breast-associated ALCL occurred in women with and without implants. Approximately 78 percent of cases (21 of 27) were $CD30^+$ anaplastic lymphoma kinase–negative, with an indolent clinical course. Both saline- and silicone-filled devices were identified; however, implant style and surface texture were largely unreported. The tumor stage at diagnosis was I in 16 of 27, II or higher in seven of 27, or unreported in four of 27. No prospective epidemiologic study has linked implants and ALCL; however, a single case-control study in Dutch women reported increased odds of association between ALCL and implants, and an estimated frequency of one in 1 million women with and without breast implants.
Conclusions: An association, without evidence of causation, was reported between breast implants and ALCL. Further study is required to confirm this association. Breast-associated ALCL occurred rarely in women with and without breast implants and had a primarily indolent clinical course, which may provoke a revision of the World Health Organization nomenclature for lymphoma; however, aggressive clinical behavior was also reported. The cases of ALCL were not confined to a specific type of implant. (*Plast. Reconstr. Surg.* 128: 651, 2011.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, V.

Breast implants were classified as class III devices by the U.S. Food and Drug Administration in 1978 after passage of the Medical Device Amendments that mandated submission of premarket approval for breast implant manufacturers in the United States.[1] In 1992, breast implant safety concerns and anecdotal reports of autoimmune disease and cancer in women with breast implants led the U.S. Food and Drug Administration to restrict the use of silicone gel–filled breast implants (except in reconstructive operations).[1–3] After an extensive evaluation of silicone gel–filled implant safety, the Institute of Medicine concluded in 1999 that there was no evidence of a causal association between silicone

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or silicone gel–filled implants and autoimmune disease or cancer.[4]

Primary lymphomas of the breast usually account for less than 1.0 percent of all non-Hodgkin's lymphoma, approximately 1.7 percent of extranodal lymphoma, and between 0.4 and 1.0 percent of patients with malignant breast neoplasms.[5] Analysis of a series of five epidemiologic studies assessing the risk of non-Hodgkin's lymphoma in women with breast implants found no association between breast implants and an increased risk of non-Hodgkin's lymphoma (standardized incidence ratio, 0.89; 95 percent confidence interval, 0.67 to 1.18).[6] Similarly, other long-term prospective epidemiologic studies have reported no association between breast implants and non-Hodgkin's lymphoma (Table 1).[6–13]

ALCL was first described in 1985 and included in the 1994 Revised European American Lymphoid Neoplasms and the 2001 World Health Organization classifications.[14] It is a rare type of lymphoma that involves a variety of tissues, including the breast, and falls within a broad category of lymphoproliferative disorders with a wide spectrum of clinical behavior (Fig. 1).[15] The two major forms of ALCL, systemic-nodal ALCL and cutaneous ALCL, together with lymphomatoid papulosis, form a spectrum of $CD30^+$ lymphoproliferative disorders. They are morphologically similar, and careful clinical evaluation and staging are required to distinguish between the two forms, as they have distinct prognoses and treatment (Fig. 2).[15,16] ALCL has been reported in women with and without breast implants.[17] Key elements of this condition among women with breast implants are malignant cells found infiltrating the periprosthetic capsule, or in a periprosthetic fluid collection.[18] Cutaneous ALCL has also been reported in women with breast implants[19]; however, as these cases of cutaneous ALCL involved the overlying breast integument and not periprosthetic breast tissue, cutaneous reports of this entity are not a subject of this review.

The differential diagnosis of ALCL is based on morphologic and immunohistochemical features and includes lymphoma-like disorder with reactive, atypical lymphoid hyperplasia, lymphomatoid papulosis, and T-cell and null-cell phenotype.[16,20] The minimum criteria required to establish a diagnosis of ALCL include malignant cytology (i.e., abnormal nuclei, prominent nucleoli), strong uniform expression of CD30, and the exclusion of epithelial malignancies (cytokeratin-negative).[16,20] Additional criteria include documentation of the t(2;5) chromosomal translocation and/or anaplastic lymphoma kinase protein overexpression and clonal T-cell receptor rearrangement.[16,20]

In this review, we examine the published literature for cases of $CD30^+$ anaplastic lymphoma kinase–negative ALCL with breast involvement (malignant cytology and/or malignant infiltration of the prosthetic tissue capsule) in women with breast implants, and critically evaluate the available evidence of an association between ALCL and breast implants.

The views, opinions, and techniques set forth in this article addressing anaplastic large cell lymphoma in women with breast implants are those of the individual author(s) and do not reflect the views, opinions, or recommendations of the American Society of Plastic Surgeons, the *Journal*, or the *Journal* editors. Any treatment recommendations contained in the article are those of the individual author(s) and are not to be considered or construed as practice guidelines, practice standards, or practice parameters. The use of any treatment technique described in the article is at the sole discretion of the physician in the exercise of his or her independent medical judgment taking into account the patient's individual circumstances.

PATIENTS AND METHODS

To identify cases of breast-associated ALCL, a PubMed search limited to English language articles was conducted for human studies or reports published from January of 1990 to October of 2010 using the search terms "breast implant" and "lymphoma," "primary T-cell breast lymphoma," or "breast implant and ALCL." Reports of primary cutaneous ALCL not involving periprosthetic breast tissue were excluded.

RESULTS

Cases of ALCL of the Breast in Patients with Breast Implants Reported in the Literature

A manual search of retrieved references revealed a total of 18 published reports describing 27 cases of ALCL in proximity to silicone gel– or saline-filled breast implants occurring either in patients without periprosthetic fluid collection ($n = 14$)[21–29] or following an initial diagnosis of late periprosthetic fluid collection occurring more than 1 year after surgery ($n = 13$)

Table 1. Epidemiologic Studies of Silicone Breast Implants and Risk of Non-Hodgkin's Lymphoma*

Reference	Size of Breast Implant Group (Comparison Group)	Study Period	Mean Follow-Up (yr)	SIR and/or RR (95% CI)	Comments
Lipworth et al., 2009[6]	3486 Swedish and 2736 Danish women with BIs (Swedish and Danish reference population)	BI dates, 1965–1993 Follow-up, 2002	16.6	SIR, 1.22 (0.56–2.32)	9 NHL cases, none with primary origin in or near breast
Deapen et al., 2007[7]	3139 women with BIs in Los Angeles (population rates)	BI dates, 1953–1980	15.5	SIR, 1.29 (0.42–3.01)	5 NHL cases
Friis et al., 2006[8]	2763 Danish women with BIs (population rates and 1736 women who had other plastic surgery)	BI dates, 1973–1995 Follow-up, 2002	14	SIR, 2.2 (0.8–4.8)	6 NHL cases RR for NHL with internal control group not listed
McLaughlin et al., 2006[9]	3486 women with implants (general population rates in Sweden)	BI dates, 1965–1993 Follow-up, 2002	18	SIR, 0.7 (0.1–1.9)	3 NHL cases
Brisson et al., 2006[10]	24,558 women with BIs in Canada (15,893 women with other cosmetic procedures and general population rates)	BI dates, 1974–1989 Follow-up, 1997	15	SIR, 0.75 (0.49–1.11) RR, 0.97 (0.53–1.76)	25 NHL cases
Brinton et al., 2001[11]	13,488 women with BIs in the United States (3936 women with other cosmetic procedures and population rates)	1960–1996	12	SIR, 0.72 (0.26–1.57) RR, 0.55 (NS)	6 NHL cases
Mellemkjaer et al., 2000[12]	1653 Danish women with BIs attending either private or public clinics (1763 women attending same clinics for other reasons and population rates)	BI dates: 1973–1995 Follow-up: 1995	Private clinic cohort: 6 Public clinic cohort: 10.3	SIR, 4.3 (0.5–15.7) for private clinic cohort SIR, 1.7 (0.0–9.3) for public hospital cohort SIR, 2.9 (0.6–8.4) for combined	3 NHL cases Overlap between this cohort and the Friis et al. and Lipworth et al. studies

BI, breast implant; CI, confidence interval; NS, not significant; RR, relative risk; SIR, standardized incidence ratio (observed cases/expected cases adjusted for age); NHL, non-Hodgkin's lymphoma.

*Adapted from 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; and Brinton LA. The relationship of silicone breast implants and cancer at other sites. *Plast Reconstr Surg.* 2007;120:94S–102S.

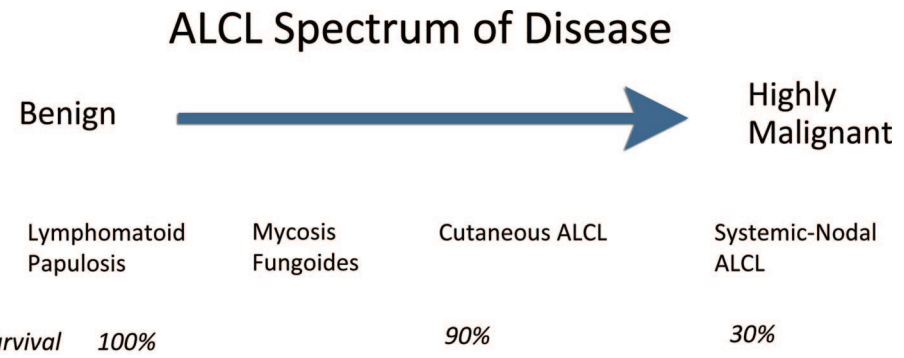

Fig. 1. Anaplastic large T-cell lymphoma (*ALCL*) lymphoproliferative CD30$^+$ spectrum of disease and clinical outcomes. (Adapted from Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood* 2005;105:3768–3785.)

(Table 2).[18,21–37] In 1997, Keech and Creech reported the first case of ALCL occurring in the periprosthetic breast tissue of a breast implant recipient.[26] Cases of non–breast implant–associated ALCL were the subject of a review by Daneshbod et al.[17] and as such are not reviewed here. In addition, as this review examines only peer-reviewed, published reports, unreported cases of ALCL in breast implant recipients may exist.

Clinical Presentation and Outcomes

The most common clinical presentation for breast-associated ALCL was unilateral breast swelling related to late (>1 year after implantation) periprosthetic fluid collection. The swollen breast was sometimes reported as painful and tender to the touch, but rarely with a mass or capsular contracture. In addition, constitutional "B" symptoms (fever, weight loss, and night sweats) were rarely reported at presentation. For the patients diagnosed with ALCL without late periprosthetic fluid, the presentation at diagnosis varied: three presented with a mass, one with pain and swelling but no fluid and two with capsular contracture. Involvement of the capsule was reported in 21 of the cases (78 percent) (Table 3).[17,18,21–37]

Patients with ALCL (with and without late periprosthetic fluid) were diagnosed at a mean age of approximately 51 years (range, 28 to 87 years). Of the 27 cases presented, 14 (52 percent) were augmentation, 11 (41 percent) were reconstruction, and two (7 percent) were unknown procedures (Table 3). The mean time interval from initial breast implant surgery to diagnosis was approximately 9 years, with a range of 1 to 23 years.[23] Of the 27 cases of ALCL (with and without late periprosthetic fluid), five cases reported implants with a specific textured surface, and 11 cases (41 percent) were in patients with a previous history of breast cancer. A majority of cases reported CD30$^+$ and anaplastic lymphoma kinase–negative immunohistochemistry (Table 3). Most patients (59 percent) had no evidence of disseminated disease and went on to be disease-free for an average follow-up of approximately 16 months (range, 7 to 48 months) after receiving therapy (Table 3).

The stage at diagnosis appeared to vary by type of presentation.[38] Among cases with information on stage presenting with late periprosthetic fluid, nine of 10 (90 percent) were stage I, whereas among cases not presenting with late periprosthetic fluid, seven of 13 (54 percent) were stage I. No peer-reviewed, published cases of breast implant–associated CD30$^+$ anaplastic lymphoma kinase–positive ALCL were retrieved. However, five cases of CD30$^+$ anaplastic lymphoma kinase–positive ALCL and six cases of CD30$^+$ anaplastic lymphoma kinase–negative ALCL were reported in patients without breast implants.[17,23] Of the women with breast implants diagnosed with ALCL of the breast (with or without late periprosthetic fluid), approximately 40 percent (11 of 27) were treated with standard non-Hodgkin's lymphoma multimodality chemotherapy [cyclophosphamide, hydroxydaunorubicin, Oncovin (Eli Lily & Company, Indianapolis, Ind.), and prednisone] with implant removal and/or capsulectomy; however, six women were treated with removal of the implant and capsulectomy alone, with one woman also receiving local irradiation after capsulectomy (Table 3). A durable complete remission (mean duration of remission of approximately 16 months) was reported regardless of treatment (Table 3). In general, in published cases, ALCL in women with breast implants behaved in an indolent clinical manner (with limited and variable follow-up),[18] which is in contrast to the aggressive clinical course of ALCL in women without implants (5-

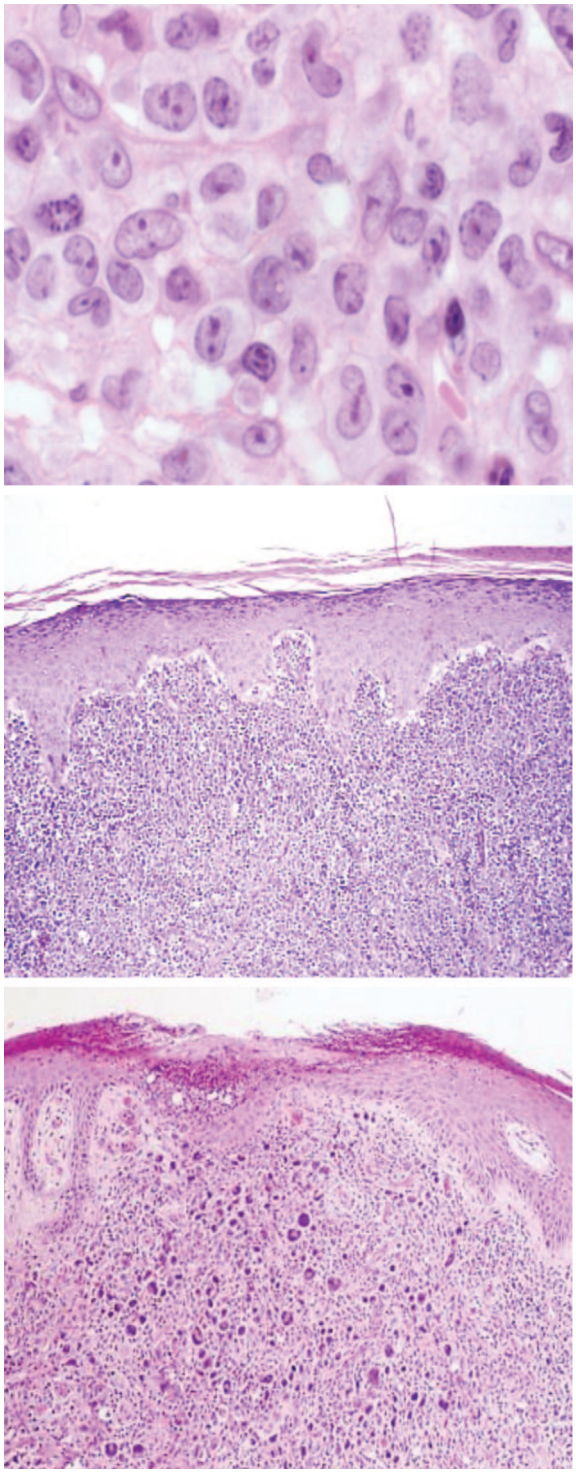

Fig. 2. Histology and immunohistochemistry of the lymphoproliferative disorders. (*Above*) Systemic nodal ALCL. A broad morphologic spectrum can be found. All cases have "hallmark cells" with eccentric horseshoe or kidney-shaped nuclei, abundant cytoplasm, large nucleoli, and convoluted nuclei "doughnut cells" or ring form cells. $CD30^+$, anaplastic lymphoma kinase–positive, epithelial membrane antigen–positive, $CD4^+$, $CD3^-$ (75 percent); variable loss of other T-cell antigens; cytotoxic proteins (granzyme B, perforin, TIA-1 present). (*Center*) Cutaneous ALCL ($CD30^+$, anaplastic lymphoma kinase–negative, epithelial membrane antigen–negative). Diffuse infiltration of the dermis, usually sparing the epidermis; infiltration of the subcutaneous; lymphocytes confined to the periphery; sheets of anaplastic, often multinucleated tumor cells ($CD30^+ > 75$ percent, $CD\ 45^+$, anaplastic lymphoma kinase–negative in 95 percent of cases); $CD4^+$ T-cell phenotype, variable loss of CD2, CD5, and/or CD3; anaplastic lymphoma kinase–negative/ epithelial membrane antigen–negative large majority of patients; T-cell clonality. (*Below*) Lymphomatoid papulosis: anaplastic cells surrounded by inflammatory cells confined to the dermis; recurrent self-healing skin lesions ($CD30^+$ less frequently positive, $CD4^+$, anaplastic lymphoma kinase–negative, clonal T-cell receptor in most cases). (Photomicrographs provided courtesy of Marshall Kadin, M.D.)

year overall survival of 15 to 45 percent in patients with anaplastic lymphoma kinase–negative systemic ALCL) despite multiagent chemotherapy (Fig. 1).[16]

Epidemiologic Studies

A total of seven studies have been published assessing the risk of non-Hodgkin's lymphoma among breast implant patient cohorts (Table 1). None of these seven prospective epidemiologic studies have established a greater number of observed non-Hodgkin's lymphoma cases in women with breast implants than expected in the general population of age-matched women. The ratio of observed cases to expected cases adjusted for age is termed the standardized incidence ratio (Table 1). A standardized incidence ratio greater than 1 indicates more observed cases than expected cases, a standardized incidence ratio of less than 1 indicates fewer observed cases than expected, and a standardized incidence ratio of 1 indicates that the number of observed cases was comparable to that expected based on population rates. The 95 percent confidence interval for the reported standardized incidence ratios in all seven studies included 1, suggesting that the observed non-Hodgkin's lymphoma cases were comparable to expected non-Hodgkin's lymphoma cases based on population rates (Table 1).

In a case-control study, de Jong et al. identified 11 patients with ALCL in the Dutch national pathology database and matched them to 35 control patients diagnosed with other lymphomas of the breast. In this analysis, five cases of ALCL occurred in women with silicone-covered, saline-filled implants, and six cases occurred in women without

Table 2. Summary of Cases in the Literature of ALCL in Women with Breast Implants*

Reference	Implant Type	Age (yr)	Presentation, Treatment, and Clinical Outcomes	Stage	Seroma and Capsule Involvement	Other Sites	CD30/ALK Status
ALCL with PPF							
Farkash et al., 2009[30]	Silicone†	54	Breast enlargement, chronic inflammatory infiltrate with fibrosis surrounding pseudocystic space; aspiration, capsulectomy, implant removal, CHOP, and irradiation; no disease at 7-mo follow-up	IA	Seroma, capsule involved	No systemic disease	NA/ALK$^-$
Olack et al., 2007[31]	Saline†	64	Enlarged, tender breast; ultrasound-guided aspiration, capsulectomy, implant removal, CHOP, and irradiation; no disease at follow-up	I	Seroma, capsule involved	No metastasis	NA/ALK$^-$
Li and Lee, 2010[32]	Silicone-covered, saline-filled†	58	Swelling with painless mass, large atypical mononuclear; MRI, aspiration, implant removal, CHOP; no disease at 10-mo follow-up	I	Seroma, capsule involved	No systemic disease	CD30$^+$/ALK$^-$
Miranda et al., 2009[29]	Silicone (NA)	65	Swelling, fluid, neoplastic cells; NA	NA	Seroma, capsule involved	NA	CD30$^+$/ALK$^-$
Newman et al., 2008[33]	Silicone‡	52	Swelling; mammography, ultrasound, aspiration, MRI, oncology consultation, CHOP, implant removal and capsulectomy after recurrence, ICE; NA	I	Seroma, capsule involved	No systemic disease	NA
Roden et al., 2008[18]	Saline, textured‡	45	Swelling; aspiration, MRI, implant removal, partial capsulectomy; no disease at 20-mo follow-up	IE	Seroma	No systemic disease	CD30$^+$/ALK$^-$
	Silicone‡	59	Swelling; aspiration, capsulectomy, radiation; no disease at 9-mo follow-up	IE	Seroma, capsule involved	No systemic disease	CD30$^+$/ALK$^-$
	Saline†	34	Breast enlargement; aspiration, bilateral implant removal, capsulectomy, CHOP, and irradiation; no disease at 9-mo follow-up	IE	Seroma, capsule involved	No systemic disease	CD30$^+$/ALK$^-$
	Silicone†	44	Swelling; aspiration, capsulectomy, implant removal; NA	NA	Seroma	NA	CD30$^+$/ALK$^-$
Sahoo et al., 2003[34]	Silicone‡	37	Breast swelling, tenderness, atypical mononuclear infiltrate; aspiration, capsulectomy, implant removal, antibiotic therapy, surgical débridement, CHOP, and irradiation; no disease at 12-mo follow-up	I	Seroma, capsule involved	No systemic disease	CD30$^+$/ALK$^-$
Hanson et al., 2010[35]	Saline, textured‡	44	Breast swelling, asymmetry, mass; capsulectomy, implant exchange; no recurrent disease	I	Seroma, capsule involved	No dissemination	NA
Do et al., 2010[36]	Silicone†	74	Nontender, mobile cystic mass; bilateral implant removal, mass excision, capsule biopsies, capsule excision, CHOP; NA	NA	Seroma, capsule involved	NA	CD30$^+$/ALK$^-$
Thompson et al., 2010[37]	Saline‡	45	Effusion surrounding implant; implant removal and capsulectomy; NA	II	Seroma	NA	NA

(*Continued*)

Table 2. (*Continued*)

Reference	Implant Type	Age (yr)	Presentation, Treatment, and Clinical Outcomes	Stage	Seroma and Capsule Involvement	Other Sites	CD30/ALK Status
ALCL without PPF							
Alobeid et al., 2009[21]	Silicone†	68	Axillary lymphadenopathy, large cell neoplasm infiltrating and expanding sinuses; capsulectomy, implant removal, CHOP; NA	II	Capsule involved	Bilateral axillary lymphadenopathy	$CD30^+/ALK^-$
Bishara et al., 2009[22]	Saline†	66	Pain, deviation toward axilla, tenderness, erythema, capsular contraction; mammogram, ultrasound, capsulectomy revealed irregular mass with some necrosis, implant removal and replacement, CHOP, and irradiation; alive at time of publication	I	Capsule involved	No systemic disease	$CD30^+/ALK^-$
de Jong et al., 2008[23]	PIP hydrogel‡	53	Large, polymorphic infiltrate of lymphoid tumor cells with small lymphocytes, macrophages, and eosinophils	I	Capsule involved	NA	$CD30^+/ALK^-$
	Textured silicone, saline-filled‡	49	Bilateral implant replacement	II	Capsule involved	NA	$CD30^+/ALK^-$
	Textured surface, silicone-filled‡	43	Unilateral implant removal	IV	Capsule involved	Right infraclavicular LN, right skull base	$CD30^+/ALK^-$
	Textured surface; silicone-filled‡	29	NA	II	Capsule involved	Right axillary LN	$CD30^+/ALK^-$
	NA‡	38	Bilateral implant replacement	IV	Capsule involved	NA	$CD30^+/ALK^-$
Fritzsche et al., 2006[24]	Silicone†	72	Skin ulcer; excision of lesion; NA	I		None	$CD30^+/ALK^-$
Gaudet et al., 2002[25]	Silicone-covered, saline-filled†	87	Mass with intense cellular infiltrate, edema, pain, warmth; ultrasound, implant removal; NA	I	Capsule involved	No systemic disease	$CD30^+/ALK^-$
	Silicone†	50	Subcutaneous nodules overlying implant; biopsy revealed infiltrate of atypical cells, CHOP; NA	I		Left lower lobe infiltrate and mediastinal lymphadenopathy 1 yr later	$CD30^+/ALK^-$
Keech and Creech, 1997[26]	Saline-filled‡	41	Mobile, nontender mass; CT scan, biopsy, CHOP, irradiation; in remission at publication	II	Capsule involved	Enlarged right axillary LN	$CD30^+$/NA
Wong et al., 2008[27]	Silicone†	40	Bilateral capsular contractures; bilateral capsulectomy and implant removal and replacement	I	Capsule involved	No systemic disease	$CD30^+/ALK^-$
Miranda et al., 2009[29]	NA‡	40	Pain and swelling, no fluid, neoplastic cells; chemotherapy and radiation; no disease at 4-yr follow-up	IIE		NA	$CD30^+/ALK^-$
Gualco et al., 2009[28]	Silicone‡	NA	Edema and swelling, mastitis; alive at 3.5-yr follow-up	NA	Capsule involved	No systemic disease	$CD30^+/ALK^-$

ALK, anaplastic lymphoma kinase; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy; ICE, ifosfamide, carboplatin, and etoposide chemotherapy; Abx, antibiotic; CT, computed tomographic; LN, lymph node; MRI, magnetic resonance imaging; NA, not available; PPF, late periprosthetic fluid; PIP, poly implant prosthesis.

*Sixteen cases of known non–breast implant–associated ALCL were reported by Daneshbod Y, Oryan A, Khojasteh HN, Rasekhi A, Ahmadi N, Mohammadianpanah M. Primary ALK-positive anaplastic large cell lymphoma of the breast: A case report and review of the literature. *J Pediatr Hematol Oncol.* 2010;32:e75–e78.

†Reconstruction following breast cancer surgery.

‡Augmentation surgery.

Table 3. Analysis of Cases in the Literature of ALCL in Patients with Breast Implants*

Characteristic	Distribution
Total no. cases of ALCL	27
Mean (SEM) age of ALCL patients, years	51.4 (9.7)
No. of PPF reported	13
Mean (SEM) time to ALCL diagnosis, years	8.9 (1.7)
Mean (SEM) duration of remission, months	15.8 (2.9)
ALCL stage, *n*	
T1N0M0 (stage 1)	16
T1N1M0 (stage 2)	6
T+N+M	1
Unknown/NA	4
Procedure, *n*	
Augmentation	12
Reconstruction	11
Revision-augmentation	2
Revision-reconstruction	0
Unknown/NA	2
Fill type, *n*	
Silicone	11
Saline	13
Hydrogel	1
Unknown	2
Surface, *n*	
Textured	5
Unknown/NA	22

NA, not available; PPF, periprosthetic fluid; SEM, standard error of the mean.

*Data from Daneshbod et al., 2010*17*; Roden et al., 2008*18*; Alobeid et al., 2009*21*; Bishara et al., 2009*22*; de Jong et al., 2008*23*; Fritzsche et al., 2006*24*; Gaudet et al., 2002*25*; Keech and Creech, 1997*26*; Wong et al., 2008*27*; Gualco et al., 2009*28*; Miranda et al., 2009*29*; Farkash et al., 2009*30*; Olack et al., 2007*31*; Li and Lee, 2010*32*; Newman et al., 2008*33*; Sahoo et al., 2003*34*; Hanson et al., 2010*35*; Do et al., 2010*36*; and Thompson et al., 2010.*37*

breast implants. From these data, with their inherent limitations,[39] an odds ratio of 18.2 (95 percent confidence interval, 2.1 to 156.8) was calculated for ALCL associated with breast implants. Despite the increased odds ratio calculated, the study concluded that the absolute risk of ALCL in patients with breast implants (and in the general population) was exceedingly low because of an estimated annual incidence of ALCL at all sites of approximately one per 1 million.[23]

DISCUSSION

ALCL is a rare form of non-Hodgkin's lymphoma that can be either cutaneous or systemic, and is a member of the lymphoproliferative $CD30^+$ spectrum of disease, with a wide range of standard treatments and clinical outcomes (Figs. 1 and 2). Case reports and one case-control study raised concerns that women with breast implants may be at a higher risk for this rare type of lymphoma. Importantly, no study has determined a causative link between implants and ALCL. However, because of the rarity of these cases, it must be acknowledged that a true association, with causation, cannot be excluded. Furthermore, the execution of a formal epidemiologic study is challenged by the rarity of consequential data. The infrequent observation of ALCL has been characterized in defined population-based studies as occurring at a similar rate of 0.1 per 100,000 in women with or without breast implants.[23] The contrast in clinical course, usually reported as indolent in women with implants and as aggressive in women without implants, is noteworthy and raises fundamental questions regarding the precision of the diagnosis. Lastly, multiple independent epidemiologic studies have reported no evidence of association between breast implants and non-Hodgkin's lymphoma.[6–12]

This review was initiated because of the anecdotal case reports of ALCL in patients with breast implants that have recently arisen in the literature. The observation that ALCL has also been reported in patients without breast implants is noteworthy.[17] This current analysis retrieved 27 published cases of ALCL (mostly anaplastic lymphoma kinase–negative ALCL) occurring in breast implant recipients.

There was no discernable pattern linking the diagnosis of ALCL to augmentative or reconstructive mammaplasty with silicone-filled or saline-filled devices. Specifically, similar proportions of patients used both saline- and silicone-filled breast implants. Implant texture was reported in only five of 27 cases, preventing determination of any pattern of association between ALCL and implant texture (Table 3).

Interestingly, despite a diagnosis of anaplastic lymphoma kinase–negative ALCL, most patients were reported to be living without disease at the last available follow-up, with some surviving patients having had only local surgical therapy (explantation and capsulectomy).[18,24] Typically, patients with anaplastic lymphoma kinase–negative ALCL have a variable and frequently unfavorable clinical outcome (with a 5-year survival rate ranging from 15 to 45 percent) when treated with standard multiagent chemotherapy. The 5-year survival rate for anaplastic lymphoma kinase–positive ALCL is comparatively better, ranging from 71 to 100 percent, for treatment with standard chemotherapy.[16] The favorable overall prognosis in the case reports reviewed suggests that the prognosis for anaplastic lymphoma kinase–negative ALCL in patients with breast implants may differ from that for patients without breast implants and may thus place this entity on the indolent end of the lymphoproliferative spectrum of disease (Fig. 1). Given the contrasting clinical outcomes between survival in women with and without

breast implants and ALCL, it is reasonable to raise the question of whether this may be a distinct clinical entity or an incorrect diagnosis in many of these reported cases. A careful review of the morphology and immunohistochemistry of ALCL on the lymphoproliferative T-cell spectrum (Figs. 1 and 2) reveals significant similarities but different clinical outcomes and standard therapy. The lack of central pathologic findings and the paradoxically good prognosis raise questions regarding the accuracy of the diagnosis. It has been suggested that the classification of ALCL and related variants, which have undergone revisions in recent years according to changing interpretations, may indeed not yet be finalized.[14]

This analysis identified 27 cases of ALCL in the published literature, which is fewer than the 34 cases identified in the recent U.S. Food and Drug Administration communication on ALCL and breast implants. A review of the U.S. Food and Drug Administration communication (based on the now published RAND report[40]) revealed that this discrepancy occurred for several reasons: (1) we excluded cases reported only in abstract form, an exclusion that is not made in the U.S. Food and Drug Administration analysis; (2) we established a slightly different case definition of $CD30^+$ anaplastic lymphoma kinase–negative ALCL with primary breast involvement (malignant cytology and/or malignant infiltration of the prosthetic tissue capsule) in women with breast implants (thus, we excluded cases of cutaneous ALCL, B-cell, or follicular lymphoma that involved the capsule or had malignant cytology in the periprosthetic fluid that were included in the U.S. Food and Drug Administration communication); (3) duplicate cases were inadvertently included; and (4) it is also important to note that our analysis included three cases not mentioned in the U.S. Food and Drug Administration communication (Hanson et al., 2010[35]; Do et al., 2010[36]; and Thompson et al., 2010[37]).

The goal of this review is to communicate the specific clinical and pathologic characteristics of cases in the peer-reviewed literature currently reporting a diagnosis described as ALCL. Subsequent scientific dialogue should refine the case definition and ultimately reach consensus as to the most accurate clinical classification. During this dialogue, many additional factors may be identified, including ALCL risk factors related to the patient (e.g., prior cancer history, psoriasis, celiac disease, human T-lymphotropic virus exposure, and human leukocyte antigen-DR types),[19,41] to the device (silicone, saline, and surface texture), and to factors mediating the interaction between the device and the patient (e.g., biofilm-producing bacteria).[42] Lastly, the careful and methodical progress of this dialogue must be driven by high-quality scientific data. Parties interested in ongoing investigations into ALCL in patients with breast implants can find information at the following web resources: www.fda.gov, www.plasticsurgery.org, www.alcldiscussion.org, and www.breastimplantsafety.org.

CONCLUSIONS

Silicone- and saline-filled breast implants remain safe for use in augmentation and reconstruction operations. Although a few cases of ALCL have been reported in patients with breast implants, an overall review of the available literature found that ALCL was rare in women with and without breast implants, occurred in women with and without prior cancer history, with different implant types, and with and without co-occurrence of late periprosthetic fluid. In addition, reported cases of ALCL generally appear to have a more indolent course than expected for anaplastic lymphoma kinase–negative ALCL. The analysis of the Danish national pathology database reported by de Jong et al. suggests that this is a rare event, without a clear association to breast implants. As a consequence, further rigorous scientific study is needed to identify any potential causal association between breast implants and ALCL. However, such study will be challenging, and may be potentially unfeasible, because of the rare occurrence (one per 1 million or less per year) of this disease. Nevertheless, such an evaluation is necessary in informing a clear case definition, and in assessing the influence of patient demographics and additional exposures, the importance of prior cancer and/or cancer treatment, and the relevance of co-occurrence of ALCL with late periprosthetic fluid.

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