Published in final edited form as:
Leuk Lymphoma. 2011 August ; 52(8): 1481–1487. doi:10.3109/10428194.2011.574755.

Primary anaplastic large-cell lymphoma associated with breast implants

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Abstract

Primary T-cell anaplastic large cell lymphoma (ALCL) of the breast is a rare entity, which has been reported in association with breast implants. In a retrospective analysis of the City of Hope pathology database, we uncovered nine such patients, eight of whom had breast implants proximal to primary ALCL. The diagnosis of ALCL in the implant capsule occurred at a median of 7 years (range 5–30) following implant surgery, and median patient age was 45.5 years (range 32–62). Malignancy was effusion-associated in 2 cases and tissue-associated in 6. Seven patients were negative for anaplastic large-cell kinase (ALK) and one patient was positive. Treatment and follow-up data were available for four patients, all tissue-associated cases: two patients were lost to follow-up after failing to mobilize stem cells and two patients were in remission, 6 years and 7.5 years post autologous transplant. These cases represent 24% of reported primary ALCL cases associated with breast implants. Our review of these cases and the literature suggest that 1) there is a strong skew in primary breast lymphomas associated with implant capsules toward T-cell, ALCL ALK-, and 2) the disease course for tissue-associated cases is not always indolent, with four patients requiring multiple treatment regimens

Keywords

ALCL; anaplastic large-cell lymphoma; breast implant; ALK^{-}

INTRODUCTION

T-cell anaplastic large-cell lymphoma (ALCL) is rare, representing only 0.75% of all lymphomas and 14% of T-cell non-Hodgkin lymphomas (NHL) reported in the United States between 1992 and 2001 [1]. Primary breast lymphomas (of various classification) are also uncommon, comprising less than 1% of all NHL and less than 0.7% of all breast malignancies [2]. Of breast NHLs, the majority are B-cell lineage, with ALCL accounting for only 6% according to a recent study [2]. In the published literature, there are 24 documented cases of primary ALCL associated with breast implants, 14 patients implanted for cosmetic reasons [3–12], 9 for reconstruction secondary to breast cancer (not lymphoma) [4,13–18], and one unknown [19] (see Table 1). Recent reports speculate on a potential association between the presence of implants and development of primary breast ALCL, and some even suggest that effusion-associated breast ALCL be defined as distinct clinical entity with an indolent course [3,11]. Roden *et al.* initially used the term seroma-associated ALCL,

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but the term effusion-associated is now preferred, as the lymphomatous fluid is not a true seroma [4].

ALCL is a distinct class of large-cell lymphomas of the T-cell or null lineage. It is characterized by cohesive proliferation of large pleomorphic blasts and CD30 antigen expression. Since 1999, expression of the anaplastic large-cell kinase (ALK) gene fusions further subdivides ALCL. ALK^+ ALCL has a better prognosis and occurs primarily in young adult males, while ALK^- ALCL occurs mostly in older adult males and females [20,21].

Multiple cases of primary ALCL of the breast, all associated with breast prostheses, were observed during patient review by the lymphoma group at City of Hope and reported at the American Society of Hematology Meeting in 2004 [22]. The presence of so many cases of primary breast ALCL at one institution was itself remarkable, and their location within the capsule of breast implants, particularly unusual. To follow up on this initial observation, we undertook a retrospective analysis of the City of Hope pathology database.

MATERIALS AND METHODS

The files of the Departments of Pathology and Hematology/Hematopoietic Cell Transplantation at the City of Hope were searched for any pathologic or clinical diagnosis of primary T cell lymphoma of the breast occurring in patients during the years 1999 – 2007. We used modified Wiseman/Liao criteria [23] for establishing primary lymphoma of the breast: adequate pathological specimen, close association of mammary tissue and lymphomatous infiltrate, and no other lymphomatous location at the time of diagnosis, excluding the presence of ipsilateral axillary lymph node involvement. Regional lymph node involvement was accepted provided that both mammary and lymph nodal lesions developed simultaneously. All patients had their pathological diagnosis established by excisional or needle biopsy, mastectomy or fine needle aspiration biopsy.

Thirteen patients had primary T-cell lymphomatous involvement of the breast with the following histological subtypes: T-lymphoblastic (1 case), high grade T-immunoblastic (1 case), T-polymorphous immunoblastic (1 case), T-diffuse large cell (1 case), and 9 cases of anaplastic large cell lymphoma. The available clinical files of all 13 patients were reviewed and 8 cases were found to be associated with breast prostheses; all 8 patients with implants had ALCL histology. For the 9 ALCL patients (including the patient with no implant), we collected demographic data, including age, history of antecedent surgeries and malignancies, and treatment type. The pathology data were also analyzed in the 9 patients, including the subtype of ALCL, immunophenotype, and molecular studies. Diagnosis of ALCL cases from the breast implants was based on the combination of cellular morphology (large, anaplastic cellular morphology) and characteristic immunophenotypic features (strong CD30 positivity, expression of T-cell associated antigens, expression of cytotoxic markers). Specimens were also tested for ALK gene expression. Some cases were further demonstrated to have arranged T-cell receptor gamma gene rearrangements.

Of these 9 primary breast ALCL cases 2 were ALK^+ and 7 were ALK^-. Eight of these nine cases (1 ALK^+ and 7 ALK^-) were associated with breast implants. Six of the implant-associated ALCL patients were seen at this institution (some as second opinions), with the remaining two diagnosed here as pathology consults but treated elsewhere. Therefore follow-up data is available for only 4 patients. The City of Hope Institutional Review Board approved the use of patient data and pathology specimens for this study.

Cytologic/Histologic and immunophenotypic studies

Fine needle aspirate preparations were stained with standard Wright-Giemsa and Pap staining for cytomorphologic evaluation. Tissue biopsy and cell block specimens were fixed in 10% buffered formalin. The specimens were then processed routinely, embedded in paraffin, and stained with hematoxylin and eosin (H&E) stain for histomorphologic evaluation. For immunohistochemistry, four-micrometer sections from paraffin-embedded blocks were immunostained with various antibodies including ALK (1:100, Dako Corporation),CD3(1:800, Dako), CD20 (1;40, Novacastra), CD15 (1:20, BD Biosciences), CD30 (1: 2,000, Dako), CD45 (1:200, Dako), EMA (1:40, Boehringer Mannheim Biochemical), granzyme B (1:50, Monosan), and perforin (1:30, Vector), using the streptavidin-biotin complex method with automated staining equipment (Dako autostainer).

T-cell Receptor Gamma Gene Rearrangements

Genomic DNA was extracted from paraffin-embedded tissues using the DNA FFPE Tissue Kit (QIAamp) according to the manufacturer's instructions. PCR procedures were performed on genomic DNA for analysis of *TRG@* (T-cell receptor gamma gene) rearrangements using four sets of specific primers. The amplified PCR products were electrophoresed under non-denaturing and denaturing conditions in 8% acrylamide gels and visualized with ethidium bromide staining. Positive cell lines (Jurkat) and plasmids were used as positive controls. The expected PCR product lengths were approximately 300bp for Vγ1–8, 220bp for Vγ9, 200bp for Vγ10 and 180bp for Vγ11 respectively. A positive result must represent a distinct band in both non-denaturing and denaturing conditions. Intrinsic control β-globin gene at 275bp was run with every sample. All positive case results were repeated one time to ensure reliability.

RESULTS

Of 13 primary T-cell primary breast lymphoma cases in the City of Hope pathology database, there were 9 ALCL patients, 8 of whom had breast implants. The one ALCL patient who did not have an implant was a 15-yr old girl who was positive for ALK staining. Table 2 shows available patient information and outcomes on the 8 patients with implants. Patient median age was 45.5 years (range 32–62). Breast involvement in our patients was left-sided in 6 patients and right-sided in 3. Implant types were usually not known, however there were 3 confirmed saline and 1 confirmed silicone type implants, and 1 was known to be texturized. Diagnosis of ALCL in the implant capsule occurred at a median of 7 years (range 5–30 years) following implant surgery. In our implant patient group, 8 patients were ALK^- and 1 patient was ALK^+.

Patient disease course, treatment recommendations and outcomes are not known for all patients; available information (summarized in Table 2) is given in greater detail below.

For patient #1, her initial complaint was swelling and fluid accumulation around the left breast. The fluid was drained and showed large atypical lymphocytes in the background of mixed small lymphocytes and histiocytes. The differential diagnosis included exuberant reactive lymphoid hyperplasia, but could not rule out a lyphoproliferative disorder. The fluid accumulation did not recur for 2 years, at which time she experienced rapid swelling of the left breast. After drainage of the fluid, cytological and immunohistochemical workup yielded a diagnosis of ALCL (ALK^-). The patient came to City of Hope for a second opinion and her diagnosis was confirmed by our pathology department. CHOP was recommended by City of Hope; however, treatment was received elsewhere and actual treatment and outcomes are unknown.

Patient #2 was a pathology consult on tissue from the fibrous capsule of the left breast implant.

Patient #3 did not initially have her implants removed, was immediately treated with 6 cycles of CHOP, but did not respond to treatment. Subsequently her implants were removed and she was treated with radiation, but her mass was increasing in size while receiving radiation. She finally achieved CR following 3 cycles of ICE salvage therapy, 11 months following initial diagnosis. Autologous transplant was recommended but there was difficulty collecting stem cells following both cyclophosphamide and then 2 more cycles of ICE priming. A matched unrelated donor search for allogeneic transplant was initiated after which the patient was lost to follow-up.

Patient #4 had received intraparenchymal silicone injections 30 years prior to diagnosis, which were replaced with implants three years later. At the time of diagnosis she had only the right implant removed, along with fluid and lymphomatous tissue from the capsule. Patient 4 was treated with 6 cycles of CHOP and radiation, but recurred in 5 months in the right breast, and was irradiated again with recurrence in 2 months, followed by cyclophosphamide treatment. After an unsuccessful attempt to collect stem cells for autologous transplant, the patient left care to pursue alternative remedies.

Patient #5 was a pathology consult on tissue from the fibrous capsule of the right breast implant.

Patient #6 found a nodule in the inframammary fold of the left breast, which grew over several months, but was negative by mammography. She had her left implant removed and the tissue in the fibrous capsule was pathologically diagnosed as ALCL. The patient was treated with 6 cycles of CHOP, but experienced tumor regrowth within 2 weeks of completion. Restaging showed systemic progression. ICE salvage was combined with radiation but was ineffective. Finally patient #6 received an autologous transplant using a cyclophosphamide/carmustine/ etoposide (CBV) conditioning regimen and had been in CR for 7.5 years post-transplant at the last recorded follow-up.

Patient #7 was diagnosed with ALCL (ALK^{-}), by excisional biopsy of a nodule from the left breast adjacent to implant. She was immediately treated with 6 cycles of CHOP after which she achieved CR. She then had her implants removed, followed immediately by radiation to the left breast. A routine PET scan 6 months after completion of radiation showed relapse in the right breast, axilla and abdomen. She was given ESHAP (etoposide, methylprednisolone, high-dose ara-C, and cisplatin) salvage, followed by stem cell collection. Following an autologous transplant, the patient has been in complete remission for 6 years.

Patient #8, presented with fluid accumulation in the left breast. After a second drainage of a large volume of fluid, while waiting for the cytology report, she had her texturized implants removed and replaced with smooth saline implants. A diagnosis of ALCL (ALK^{-}) was made and confirmed by Mayo Clinic T-cell rearrangement studies. She was CT and PET negative, except for the left breast and had no B symptoms. The patient came to City of Hope for a second opinion as she was reluctant to start chemotherapy, and her diagnosis was confirmed based on pathology. Treatment with CHOP was recommended, but she was treated elsewhere, and treatment and outcome were unknown.

DISCUSSION

We report on 8 implant-associated cases of primary breast ALCL, from a pool of 9 total cases of primary breast ALCL, and 13 total cases of primary T-cell lymphoma of the breast, from the City of Hope pathology database. Of these 8 implant-associated ALCL cases, 7

were ALK^- and 1 was ALK^+. Breast lymphomas are rare, and typically of B-cell origin, with only 6% typically of ALCL histology [2]. The association with implants of 8/9 cases of primary breast ALCL at this institution, is extraordinary. In addition all 7 cases of ALK^- ALCL were associated with breast implants.

The median patient age in this series, of 45.5 years (32–62), is similar to the median age of 47.5 years (range 28–87) for the 24 ALCL implant-associated cases found in the literature (see Table 1). Both of these ALCL median ages are lower than the previously characterized median age of 57.6 (for 96 patients) in a prospective study of primary breast lymphoma [24]. The median age for systemic ALCL differs significantly depending upon expression of the anaplastic lymphoma kinase (ALK). The median age of ALK^+ patients is 30 years and 61 years for ALK^- patients [21]. With 7/8 of our patients testing ALK^-, the median age is much lower than expected. The presence of one ALK^+ patient with an implant is unusual, since cases reported in the literature are ALK^-, but we have no explanation for this distinction.

As most of the implants were not removed at City of Hope, we were only able to confirm implant type in four patients: three were saline and one silicone. Of the 24 cases of primary breast implant-associated ALCL in the literature, 11 implants are silicone, 9 are saline, 1 hydrogel, and 3 are of unknown composition. The median time span from implant surgery to diagnosis of ALCL was 7 years (range 1–23 yrs) in the literature, the same as our median of 7 years. Twenty of twenty-four primary implant-associated ALCL cases in the literature report ALK^-, with 4 cases of unknown ALK status; at City of Hope, 7 patients are ALK^- and 1 patient was ALK^+.

Outcomes for primary implant-associated breast ALCL are recorded in only 10 of 24 published cases, many of which are in pathology or plastic surgery publications. Only two patients were reported to have relapsed after initial treatment; one achieved CR post capsulectomy (effusion-associated) [6] and the other metastasized to the lungs and pericardium (tissue-associated) [8]. One report of 4 patients from the Mayo Clinic describes seroma-associated ALK^- breast implant ALCL as an indolent T-cell proliferative disorder in contrast to usual ALK^- ALCL [4]. As several of the patients in our study were seen for diagnosis confirmation and treated elsewhere, we are unable to make definitive conclusions regarding aggressiveness of the lymphoma. Based on the four patients for whom we do have follow-up information, the disease course appears to be moderately aggressive, with relapse in weeks to months after treatment.

In studies that report on broad categories of malignancy, such as breast cancer and NHL, most show no increase, or in fact, a decrease in the risk of breast malignancy associated with implants [25–29]. De Jong *et al.* report an odds ratio of 18.2 for association of breast implants with breast ALCL based on data from a national registry in the Netherlands, however they note that absolute risk remains low due to the rarity of breast ALCL [3].

As a tertiary care institution, it is difficult to extrapolate our incidence numbers to the general population and epidemeological information from the Los Angeles County Department of Health does not include histological subtype for lymphomas. The City of Hope breast cancer program gives access to a large pool of women that have received implants for reconstruction post-mastectomy and our proximity to Los Angeles, which has a high per capita rate of cosmetic surgery [30], may also contribute to the incidence frequency. Without epidemiological data, we cannot comment on the risk of primary breast implant-associated ALCL; however, eight of nine cases of primary breast ALCL cases found in association with breast implants is notable for a single institution. We can draw two main conclusions from this patient case series: 1) there is a strong skew toward the ALCL ALK^-

histology in the occurrence of primary T-cell lymphomas associated with breast implants, and 2) the disease course is not always indolent in patients with tissue-associated disease, with several patients requiring multiple treatment regimens. A large multi-center prospective study would be required to answer questions regarding relationships between implants and ALCL of the breast. During the revision of this manuscript, the FDA has issued a preliminary finding regarding the possible connection between breast implants and ALCL [31] They have cited multiple occurrences in the literature as well as events recorded via adverse event reporting by implant manufacturers, to support an increased risk of ALCL in women with implants. The FDA is establishing a registry to allow further study of this association and is requesting physicians to report any confirmed cases of ALCL in patients with breast implants. As more cases are reported in the literature and there are a large number of women receiving cosmetic implants, it is especially important to carefully discriminate between ductal carcinoma and tissue-associated ALCL in the differential diagnosis of breast malignancy in women with implants.

Acknowledgments

This study was supported in part by grant # P50 CA107399 from the National Institute of Health and also by the Tim Nesvig Lymphoma Research Fund.

REFERENCES

1. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001. Blood. 2006; 107:265–276. [PubMed: 16150940]
2. Talwalkar SS, Miranda RN, Valbuena JR, Routbort MJ, Martin AW, Medeiros LJ. Lymphomas involving the breast: a study of 106 cases comparing localized and disseminated neoplasms. Am J Surg Pathol. 2008; 32:1299–1309. [PubMed: 18636016]
3. de Jong D, Vasmel WL, de Boer JP, Verhave G, Barbe E, Casparie MK, van Leeuwen FE. Anaplastic large-cell lymphoma in women with breast implants. Jama. 2008; 300:2030–2035. [PubMed: 18984890]
4. 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. [PubMed: 18223553]
5. Gualco G, Bacchi CE. B-cell and T-cell lymphomas of the breast: clinical--pathological features of 53 cases. Int J Surg Pathol. 2008; 16:407–413. [PubMed: 18480397]
6. Newman MK, Zemmel 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. 2008; 61:822–825. [PubMed: 17509956]
7. 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. [PubMed: 12653596]
8. Keech JA Jr, Creech BJ. Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant. Plast Reconstr Surg. 1997; 100:554–555. [PubMed: 9252643]
9. Said JW, Tasaka T, Takeuchi S, Asou H, de Vos S, Cesarman E, Knowles DM, Koeffler HP. 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; 88:3124–3128. [PubMed: 8874212]
10. 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. [PubMed: 18594466]
11. Thompson PA, Lade S, Webster H, Ryan G, Prince HM. Effusion-associated anaplastic large cell lymphoma of the breast: time for it to be defined as a distinct clinico-pathological entity. Haematologica. 2010; 95:1977–1979. [PubMed: 20801901]

12. Lechner MG, Lade S, Liebertz DJ, Prince HM, Brody GS, Webster HR, Epstein 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. 2010 n/a-n/a.
13. 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. [PubMed: 17589261]
14. Fritzsche FR, Pahl S, Petersen I, Burkhardt M, Dankof A, Dietel M, Kristiansen G. 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. [PubMed: 16983530]
15. 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. [PubMed: 11908714]
16. 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. [PubMed: 19330656]
17. 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. [PubMed: 19341480]
18. Li S, Lee AK. Silicone implant and primary breast ALK1-negative anaplastic large cell lymphoma, fact or fiction? Int J Clin Exp Pathol. 2009; 3:117–127. [PubMed: 19918336]
19. Miranda RN, Lin L, Talwalkar SS, Manning JT, Medeiros LJ. Anaplastic large cell lymphoma involving the breast: a clinicopathologic study of 6 cases and review of the literature. Arch Pathol Lab Med. 2009; 133:1383–1390. [PubMed: 19722744]
20. Stein H, Foss HD, Durkop H, Marafioti T, Delsol G, Pulford K, Pileri S, Falini B. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood. 2000; 96:3681–3695. [PubMed: 11090048]
21. Gascoyne RD, Aoun P, Wu D, Chhanabhai M, Skinnider BF, Greiner TC, Morris SW, Connors JM, Vose JM, Viswanatha DS, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood. 1999; 93:3913–3921. [PubMed: 10339500]
22. Popplewell LL, Chang K, Olevsky O, Nademanee A, Forman S. Primary anaplastic large cell lymphoma of the breast occurring in patients with silicone breast implants. Blood. 2004; 104 abstr# 4563.
23. Wiseman C, Liao KT. Primary lymphoma of the breast. Cancer. 1972; 29:1705–1712. [PubMed: 4555557]
24. Aviles A, Delgado S, Nambo MJ, Neri N, Murillo E, Cleto S. Primary breast lymphoma: results of a controlled clinical trial. Oncology. 2005; 69:256–260. [PubMed: 16166814]
25. Brinton LA, Brown SL. Breast implants and cancer. J Natl Cancer Inst. 1997; 89:1341–1349. [PubMed: 9308703]
26. Brinton LA, Lubin JH, Murray MC, Colton T, Hoover RN. Mortality rates among augmentation mammoplasty patients: an update. Epidemiology. 2006; 17:162–169. [PubMed: 16477256]
27. Friis S, Holmich LR, McLaughlin JK, Kjoller K, Fryzek JP, Henriksen TF, Olsen JH. Cancer risk among Danish women with cosmetic breast implants. Int J Cancer. 2006; 118:998–1003. [PubMed: 16152592]
28. 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. [PubMed: 19319041]
29. 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. [PubMed: 16622125]
30. Ruiz, R. America's Vainest Cities Forbes.com. 2007. p http://www.forbes.com/2007/11/29/plastic-health-surgery-forbeslife-cx_rr_1129health.html.

31. Anaplastic Large Cell Lymphoma (ALCL) In Women with Breast Implants: Preliminary FDA Findings and Analyses [Internet]: US Food and Drug Administration; 2011. Available from: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239996.htm

Table 1

Primary breast ALCL patients in the literature

Pt	Author	Cosmetic or Reconstr	Age	Yrs post-implant	ALK status	Effusion- or Tissue-associated	Implant type	Treatment	Outcome
1	Lechner/Thompson 2010 [11,12]	cosmetic	42	3	neg	Effusion	saline-filled, silicone shell NAgor	radiation	CR 7m
2	Li 2009 [18]	reconstr	58	5.5	neg	Tissue	saline-filled, silicone-walled	CHOP	CR 10 m
3	Bishara 2009 [17]	reconstr	66	12	neg	Tissue	saline	NA	NA
4	Alobeid 2009 [16]	reconstr	68	16	neg	Tissue	silicone	CHOP	NA
5	Miranda 2009 [19]	NA	65	NA	neg	Effusion	NA	NA	NA
6	Wong 2008 [10]	cosmetic	40	19	neg	Tissue	silicone	CHOP/rad	NA
7	deJong 2008 [3]	cosmetic	53	1	neg	NA	PIP Hydrogel, silicone-walled	NA	NA
8	deJong 2008 [3]	cosmetic	49	23	neg	NA	texturized silicone McGhan	NA	NA
9	deJong 2008 [3]	cosmetic	43	13	neg	Tissue	texturized silicone McGhan	NA	NA
10	deJong 2008 [3]	cosmetic	29	7	neg	Tissue	texturized silicone NAgor R	NA	NA
11	deJong 2008 [3]	cosmetic	38	13	neg	NA	NA	NA	NA
12	Roden 2008 [4]	reconstr	45	7	neg	Effusion	saline	No	CR 20 m
13	Roden 2008 [4]	reconstr	59	3	neg	Effusion	silicone	Radiation	CR 10 m
14	Roden 2008 [4]	cosmetic	34	4	neg	Effusion	saline	CHOP/radiation	CR 9 m
15	Roden 2008 [4]	cosmetic	34	NA	neg	Effusion	saline	NA	NA
16	Newman 2008 [6]	cosmetic	52	14	NA	Effusion	silicone gel M cG han	CHOP/surg/ICE	Relapse, CR 2 yr
17	Gualco 2008 [5]	cosmetic	28	6	NA	Tissue	NA	NA	NA
18	Olack 2007 [13]	reconstr	64	7	neg	Effusion	saline	CHOP	CR 2 yr
19	Fritzsche 2006 [14]	reconstr	72	16	neg	Tissue	polyurethane-coated silicone	No	NA
20	Gaudet 2002 [15]	reconstr	87	7	neg	Tissue	saline-filled, silicone-walled	NA	NA
21	Gaudet 2002 [15]	reconstr	50	9	neg	Tissue	silicone gel-filled	CHOP	Relapse, metastasis
22	Sahoo 2002 [7]	cosmetic	33	5	neg	Effusion	double lumen silicone	CHOP/radiation	CR 1 yr
23	Keech 1997 [8]	cosmetic	41	5	NA	Tissue	texturized saline McGhan	CHOP/radiation	CR 1 yr
24	Said 1996 [9]	cosmetic	46	5	NA	Effusion	silicone	NA	NA

Reconstr = reconstructive, NA = information not available, neg = negative (ALK^-), CHOP = cyclophosphamide/doxorubicin/ vincristine/prednisolone, surg = surgery, ICE = ifosfamide/carboplatin/ etoposide, CR = complete remission, m = month, yr = years

Table 2

City of Hope Patient Data

Pt	Age*	Cosmetic or Reconstr	Yrs post-implant	ALK +/−	Effusion- or Tissue-associated	Implant status	Treatment	Outcome
1	49	cosmetic	5 yrs	neg	Effusion	saline	CHOP recom m ended	NA
2	42	NA	NA	neg	Tissue	NA	NA	NA
3	41	cosmetic	12	neg	Tissue	removed	CHOP, ICE, CY, ICE, MUD search	LTF
4	62	cosmetic	30	neg	Tissue	silicone injection, then implants, rt removed	CHOP, radiation, C Y, relapse, then alternative medicine	Relapse /LTF
5	49	NA	NA	neg	Tissue	NA	NA	
6	54	cosmetic	9	neg	Tissue	removed	CHOP, ICE/radiation, auto	CR 7.5 years
7	41	cosmetic	5 yrs	pos*	Tissue	saline, removed, replaced, removed	CHOP, radiation, relapse, ESHAP, auto	CR 6 years
8	32	cosmetic	5 yrs	neg	Effusion	McGhan texturized, replaced wsaline	CHOP recommended	NA

*first tissue sample recorded ALK^-subsequent test on same tissue and subsequent tissue sample both tested ALK^+ neg = negative (ALK^-), pos = positive (ALK^+), NA = information not available, rt = right, CHOP = cyclophosphamide/doxorubicin/vincristine/prednisolone, CY + cyclophosphamide, ICE = ifosfamide/carboplatin/etoposide, MUD = matched unrelated donor allogeneic transplant, auto = autologous transplant, ESHAP = etoposide/methylprednisolone/high-dose ara-C/cisplatin, LTF = lost to follow-up, CR = complete remission