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B-cell lymphomas associated with breast implants: Report of three cases and review of the literature

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ABSTRACT

Since the first reported case in 1997, over 600 women with breast implant-associated anaplastic large cell lymphoma (BI ALCL) have been reported. BI ALCL is a CD30-positive T-cell lymphoma that carries clonal T-cell receptor gene rearrangements, and a subset of cases harbors mutations in the JAK-STAT signaling pathway. Rarely, other histologic types of lymphoma have been reported in association with breast implants, including fewer than 10 cases of B-cell origin. Here, we describe three additional patients with B-cell lymphoma occurring around breast implants. Two of these patients developed extranodal marginal zone lymphoma in the peri-implant capsule, one of which had a concurrent ALCL within the superficial lining of the capsule. The third patient presented with diffuse large B-cell lymphoma inside the breast parenchyma surrounding her implant. Determining the etiology and risk factors for the development of B-cell lymphomas associated with breast implants remains challenging, given the wide spectrum of histologic features and the rarity of these neoplasms. Ultimately, we document three new cases of B-cell lymphoma arising around breast implants and highlight their clinical and pathologic features in order to expand our understanding of this rare disease presentation.

1. Introduction

The first silicone, gel-filled breast prostheses were placed in 1962, and the widespread acceptance of this procedure for cosmetic and reconstruction purposes has resulted in an average of 300,000 breast implantations per year for cosmetic reasons in the United States [1,2]. Until the 1990s, the increased risk of malignancy associated with breast implants remained uncertain. Keech and Creech described the first case of breast implant-associated anaplastic large cell lymphoma (BI ALCL) in 1997 [3], now recognized by the World Health Organization (WHO) [4,5]. However, it is likely that these cases occurred earlier [6], highlighting the use of textured implants since 1990 as a likely cause of BI ALCL [7-9]. As the disease has been better defined and accepted, the reported number of affected patients has increased; current risk estimates for developing this lymphoma range between 1 in 3817 to 30,000 persons who receive textured implants [10-12], and even higher if the study cohort is restricted to a dedicated cancer center [13]. BI ALCL is a CD30-positive T-cell lymphoma associated with clonal T-cell receptor gene rearrangements. A subset of cases is associated with mutations of the JAK-STAT signaling pathway, but the pathogenesis of this neoplasm is still poorly understood.

Anecdotal cases of other histologic types of lymphoma involving the breast capsule have been reported, such as extranodal NK/T-cell lymphoma, nasal type [14], and six cases of B-cell lymphoma including follicular lymphoma [15], intravascular large-cell lymphoma [16], diffuse large B-cell lymphoma [17], marginal zone lymphoma [18,19], and plasmablastic lymphoma [20]. With such a limited number of patients, an analysis of the epidemiologic features and underlying

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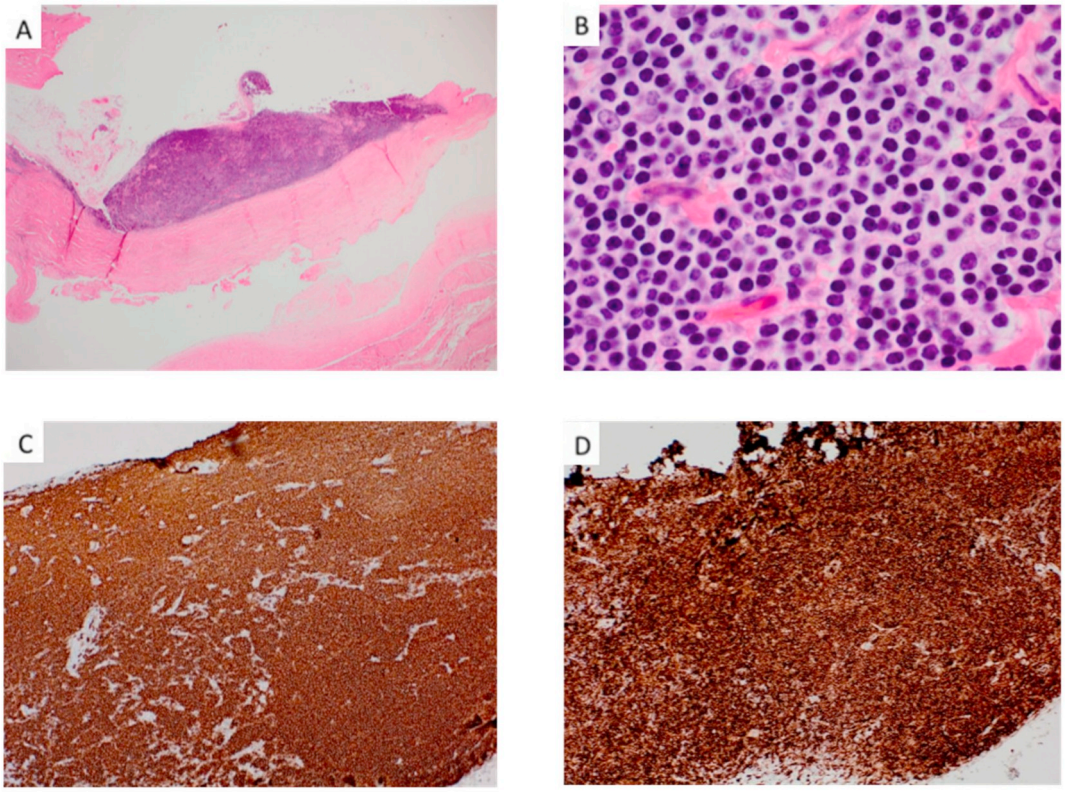

Fig. 1. Case 1: The patient's breast capsule features a diffuse infiltrate on the luminal side, composed of hyperchromatic, small lymphocytes (A, hematoxylin and eosin, 20×); high magnification (B, hematoxylin and eosin, 400×). Immunohistochemistry shows that almost all of the lymphocytes are positive for the B-cell marker CD20 (C, 200×), with co-expression of CD43 (D, 200×). These findings support the diagnosis of extranodal marginal zone lymphoma.

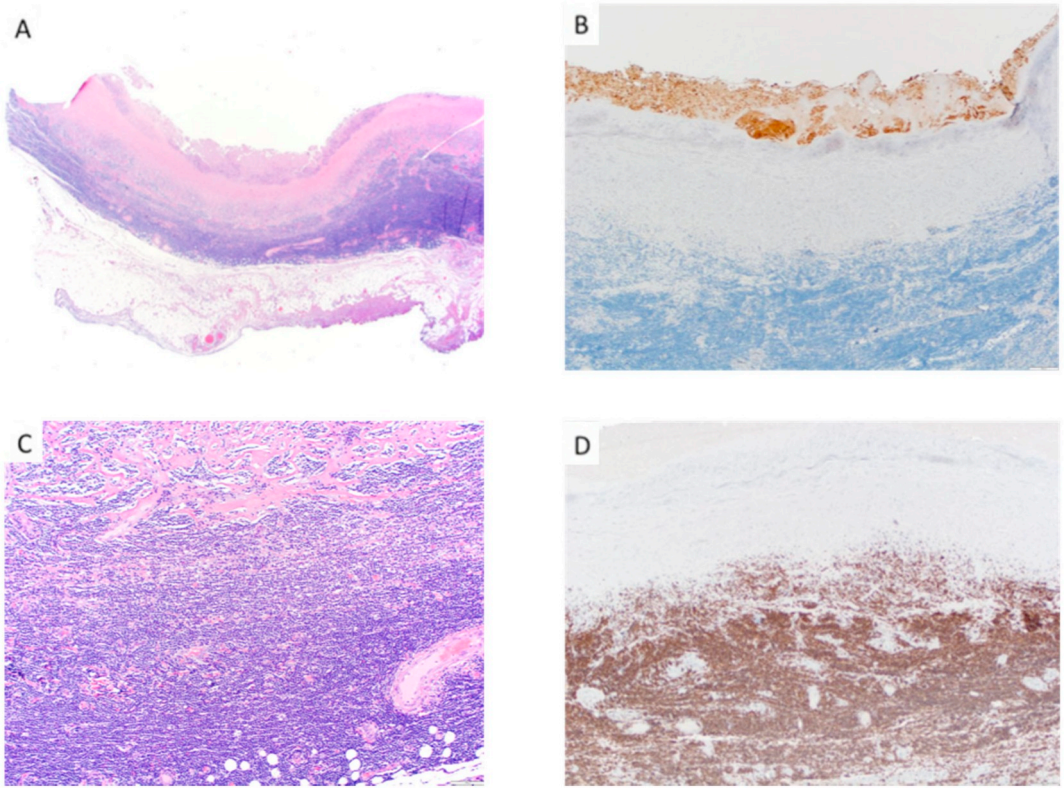

Fig. 2. Case 2: The breast capsule is thickened with a necrotic luminal side, and a dense lymphocytic infiltrate on the opposing side (A, hematoxylin and eosin, 10×). Immunohistochemistry with anti-CD30 stains the larger neoplastic cells at the luminal side, supporting the diagnosis of anaplastic large cell lymphoma (B, 40×). The deeper infiltrate is composed of small lymphocytes with oval-to-round, hyperchromatic nuclei (C, hematoxylin and eosin, 100×). Immunohistochemical staining for anti-CD20 highlights most of these lymphocytes, indicating a B-cell lymphoma (D, 40×).

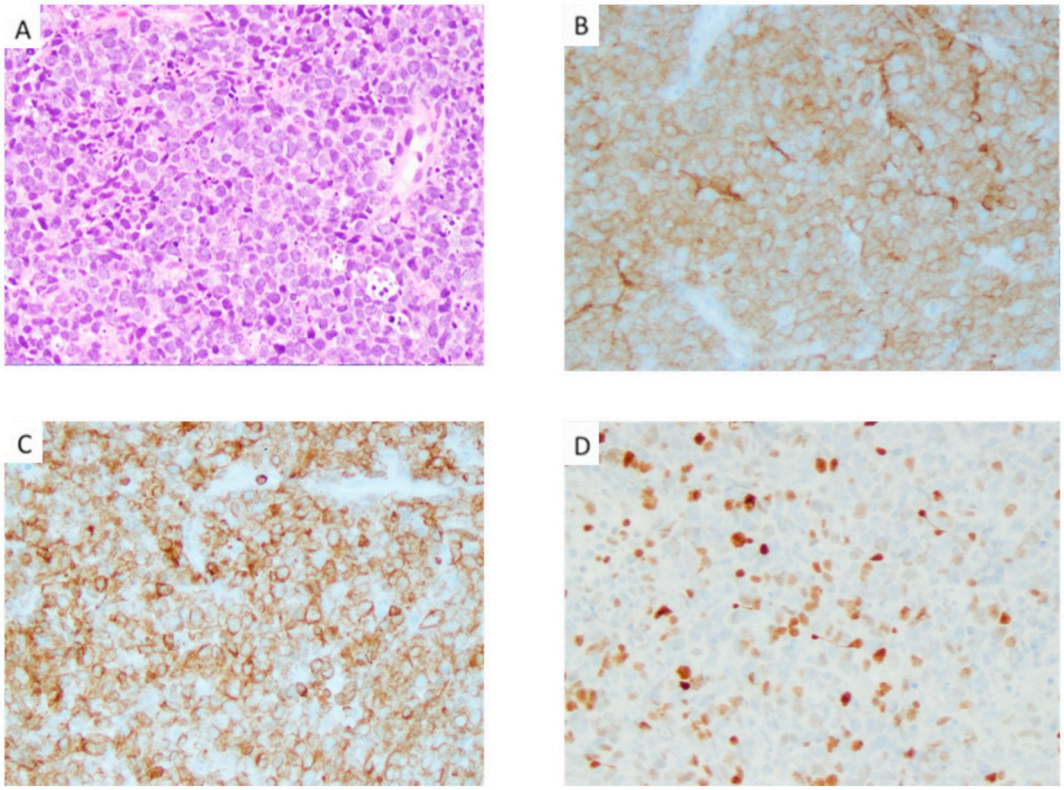

Fig. 3. Case 3: Core biopsy of the breast mass reveals a diffuse infiltrate of large lymphoid cells with irregular nuclear contours, vesicular chromatin, and occasional conspicuous nucleoli (A, hematoxylin and eosin, 200×). Immunohistochemistry for the germinal center cell marker CD10 demonstrates that most of the cells are positive (B, 200×). The cells also stain positive for the antiapoptotic marker BCL2 (C, 200×). Staining for the oncogenic marker c-MYC is positive in approximately 30% of the cells (D, 200×). The rendered diagnosis was diffuse large B-cell lymphoma, germinal center subtype.

mechanisms that may explain pathogenesis are not possible at this time.

Here, we describe an additional three women who developed a B-cell lymphoma within the capsular tissue surrounding breast implants. We also review the literature in an attempt to determine the clinicopathologic features of these neoplasms.

2. Case 1

A 62-year-old Caucasian woman with a history of silicone breast augmentation at the age of 26 and revision at age 37, noted recent, progressive right-breast swelling and discomfort. Physical examination did not reveal lymphadenopathy, hepatosplenomegaly, breast masses, or nipple discharge. Screening mammography showed bilateral, benign-appearing calcifications without suspicious masses or areas of unexplained distortion. She underwent bilateral implant removal and capsulectomy. During the procedure, plaques of frothy granulation tissue were noted in the right breast capsule, clinically suggestive of an inflammatory response. However, cultures from fluid sampled intraoperatively were negative, and the implants appeared to be intact. Microscopic review demonstrated a dense infiltrate of small, hyperchromatic lymphocytes within the right breast capsule. Immunohistochemistry showed that the lymphocytes were positive for CD20 and CD43, with kappa light chain restriction (Fig. 1), and were negative for CD5 and CD10. The left capsule revealed mild chronic inflammation and small lymphoid aggregates not suspicious for lymphoma. She was diagnosed with stage IE extranodal marginal zone lymphoma associated with the breast implant capsule. Treatment involved explantation alone. PET-CT scans after implant removal and complete capsulectomy were unremarkable, and the patient was free of disease 29 months after diagnosis.

3. Case 2

A 69-year-old Caucasian woman with a history of left-sided stage II estrogen receptor-positive breast cancer, status post mastectomy and textured saline implant placement, chemotherapy, and tamoxifen therapy, presented 13 years later with months of left-sided breast swelling and pain. Breast MRI demonstrated an intact implant surrounded by a large volume of fluid and a thickened fibrous capsule with dependent debris. The patient elected for implant removal and complete left capsulectomy, as well as prophylactic right-sided mastectomy. Cytologic examination of the peri-implant fluid revealed large pleomorphic cells with lobated nuclei and abundant vacuolated cytoplasms. The capsulectomy specimen was thickened, fibromembranous, and without a discrete lesion. Microscopic examination of the capsule demonstrated necrotic and fibrinoid material on the luminal side adjacent to the implant, as well as small clusters of large, pleomorphic cells with folded nuclei, vesicular chromatin, and abundant cytoplasm confined to the superficial capsular surface. Immunohistochemical testing showed that the large cells were strongly positive for CD30 and negative for anaplastic lymphoma kinase (ALK) (Fig. 2).

In addition, the deeper portion of the capsule was diffusely and uniformly infiltrated by small, round-to-oval, hyperchromatic lymphocytes; no karyorrhexis or necrosis was observed. By immunohistochemistry, the small lymphocytes were positive for CD45RB/leukocyte common antigen and CD20, but were negative for CD3, CD5, CD10, CD30, CD43, and CD68, consistent with extranodal marginal zone lymphoma (Fig. 2). An axillary lymph node excised during the patient's right-sided prophylactic mastectomy was diffusely infiltrated by marginal zone lymphoma. Subsequent bone marrow aspiration and biopsy demonstrated 60% involvement by the marginal zone lymphoma, with no abnormal T cells noted. The patient was referred for oncologic evaluation and no additional therapy was recommended for

Table 1
Patients with of B-cell lymphomas involving the capsular tissue around breast implants; review of the literature and addition of 3 new cases.

Study	Age (years)	Implant surface	Implant filling	Time from implantation to lymphoma (years)	Lymphoma diagnosis	Presentation	Location	Treatment	Outcome
Cook et al. 1995	56	Polyurethane	Silicone	6	Follicular lymphoma	Palpable mass and contracture	Left breast capsule and bone marrow	Mass resection, contracture correction, implant replacement	Unknown
Smith et al. 2014	83	Smooth Arion	Silicone	44	DLBCL associated with chronic inflammation	Swelling and fluid surrounding right breast	Right breast capsule	Implant removal and complete capsulectomy	Relapse at 3 years, DFS[c] at 84 months
Moling et al. 2016	48	Polytech 44-G	Silicone	4	Intravascular large B-cell lymphoma, hemophagocytic syndrome-associated form (Asian variant)	Fever, splenomegaly, and hemophagocytic lymphohistiocytosis	Right breast capsule	Implant removal, partial capsulectomy, R-CHOP[a], intrathecal methotrexate	DFS[c] at 21 months
Chen et al. 2018	34	Poly-implant prosthesis (PIP)	Silicone	14	Low-grade B-cell lymphoma/ extranodal marginal zone lymphoma	Recurrent capsular contracture	Right and left breast capsule	Implant removal, mastectomy, complete capsulectomy, rituximab	DFS[c] at 24 months
Har-Shai et al. 2019 & 2020	59	Textured NAGOR	Silicone	11	Anaplastic large cell lymphoma and extranodal marginal zone lymphoma	Swelling and fluid surrounding left breast	Left breast capsule	Implant removal and complete capsulectomy	Persistent extranodal marginal zone lymphoma at 20 months
Geethakumari et al. 2019	74	Unknown	Saline	40	Plasmablastic lymphoma	Pain, swelling, and fluid surrounding left breast	Left breast capsule	Implant removal, complete capsulectomy, V-EPOCH[b] + bortezomib, consolidative radiation	DFS[c] at 12 months
Current study Case 1	62	Textured McGhan	Silicone	36	Extranodal marginal zone lymphoma	Swelling and fluid surrounding right breast	Right breast capsule	Implant removal and complete capsulectomy	DFS[c] at 29 months
Current study Case 2	69	Textured McGhan	Silicone	13	Anaplastic large cell lymphoma and extranodal marginal zone lymphoma	Swelling and fluid surrounding left breast	Left breast capsule	Implant removal, complete capsulectomy, bendamustine + rituximab	DFS[c] at 60 months
Current study Case 3	61	Textured Additional information unknown	Saline	21	Diffuse large B-cell lymphoma	Swelling and painful mass	Right breast capsule and parenchyma	R-CHOP[a], intrathecal methotrexate	Status post 6 cycles of with complete response

[a] Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.
[b] Vincristine plus etoposide, cyclophosphamide, doxorubicin, and prednisone.
[c] Disease free survival.

the ALCL. However, for the marginal zone lymphoma she received two doses of bendamustine plus rituximab, followed by a four-week induction course of single agent rituximab and two-year maintenance. In the five years since completing this therapy, the patient has remained without radiologic or clinical evidence of disease.

4. Case 3

A 61-year-old Caucasian woman with a history of breast augmentation with saline textured implants presented 21 years after the procedure with a right-breast mass that had been enlarging over six weeks. She denied nipple discharge, breast trauma, fever, or other constitutional symptoms, but was concerned that the mass was distorting her nipple appearance. Physical examination demonstrated edema and erythema of the right breast with mild skin induration. Ultrasound imaging revealed a complex cystic and solid mass at 12 o'clock, measuring nine centimeters in greatest dimension and extending into the patient's peri-implant breast capsule.

Core biopsies of the mass featured a diffuse infiltrate of large atypical lymphocytes with irregular nuclear contours and occasional conspicuous nucleoli, with frequent mitoses and apoptotic bodies. Immunohistochemical analysis showed that the cells were positive for CD10, CD20, BCL6, MUM1, BCL2, and c-MYC (~30%) and negative for CD3 and TdT (Fig. 3). Ki-67 demonstrated a high mitotic index of 95–100%, and *in situ* hybridization was negative for Epstein-Barr virus-encoded RNA (EBER). The findings supported the diagnosis of diffuse large B-cell lymphoma, germinal center subtype. Conventional cytogenetic analysis was notable for gains of chromosomes 8q, 14q, and 18q. Subsequent bone marrow and right axillary lymph node biopsy specimens were uninvolved by the patient's malignancy. The patient received 6 cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with complete resolution of her breast mass.

5. Discussion

Including the three we describe, nine cases of B-cell lymphoma associated with breast implant capsules have been reported. Their features are summarized in Table 1. The age range for these patients is 34 to 83 years with a median age of 61 years. Five lymphomas involved the left side and four the right. In seven patients the implants were silicone and in two saline; the implant surfaces were variable. The interval from implant placement to B-cell lymphoma ranged from 4 to 40 years. Histologic classification of these neoplasms included: 4 extranodal marginal zone lymphoma, 2 diffuse large B-cell lymphoma, 1 follicular lymphoma, 1 plasmablastic lymphoma, and 1 intravascular large B-cell lymphoma. A diversity of presentations and treatments were documented. All patients were alive at last follow up.

From this group we excluded a report by Said et al. of primary effusion lymphoma [21], since a recent reassessment of that case suggests that the diagnosis was more likely BI ALCL [6]. One of the patients we describe (Case 2) had composite BI ALCL and extranodal marginal zone lymphoma, and a review of the literature revealed that Har-Shai et al. has reported a similar case [19,22]. These authors presented a 59-year-old woman who developed the two lymphomas simultaneously around a textured silicone implant 11 years after augmentation surgery. The breast capsule of this patient demonstrated striking similarities to the microscopic features in our current case. Bone marrow involvement by marginal zone lymphoma was also present. In contrast, our patient also demonstrated B-cell lymphoma in an axillary lymph node, leading to the administration of chemotherapy. The previously reported individual had persistent marginal zone lymphoma at last follow up, but the patient we report has shown no evidence of disease five years after treatment.

Typically, more than 90% of lymphomas arising around breast implants are BI ALCL. Although studies such as those published by Brinton et al. concluded no increased risk of non-breast malignancies in patients with implants, the increasing body of literature on this topic supports the association between implantation and the development of ALCL [23,24]. The etiology of BI ALCL is not entirely understood.

Implant texturing has been implicated in the pathogenesis of BI ALCL [11]. Hu et al. indicated that textured implants harbor biofilm-producing bacteria, which could trigger lymphocyte activation [[25]]. The study specifically demonstrated that BI ALCL was associated with CD4-positive T cells with an antigen-driven, memory Th1/Th17 phenotype. Essentially, sustained response to capsular bacteria could provide the inflammatory microenvironment in which BI ALCL can arise. Since Allergan's Biocell textured implants have been implicated in more than half of the reported cases of BI ALCL in which implant texture was known, the United States Food and Drug Administration supported a worldwide recall of this product in July of 2019 [[26]].

Establishing similar causation between breast implants and B-cell lymphomas is highly challenging, given the limited number of B-cell lymphoma cases associated with breast implants reported. However, these nine published cases raise the possibility that the occurrence of B-cell lymphomas around breast implants is not simply coincidental. In particular, extranodal marginal zone lymphoma has been observed at other tissue sites as a response to antigen stimuli from invasive pathogens. For example, *Helicobacter pylori*, *Borrelia burgdorferi*, and *Chlamydia psittaci* have been associated with gastric, cutaneous, and ocular B-cell lymphomas, respectively [[27]]. One might therefore hypothesize that the proinflammatory environment provided by bacterial-laden textured implants potentiated B-cell proliferations in the reported patients. Notably, all but one of the patients we have discussed had textured breast prostheses. Smith et al. reported a woman who presented with effusion around 44 years after reconstruction with smooth silicone implants, apparently challenging the theory that only textured implants result in the development of B-cell lymphoma [17]. In effect, that case is most specifically classified as diffuse large B-cell lymphoma associated with chronic inflammation, recently described by the WHO [[28]]. Ultimately, our study contributes to a limited yet growing body of literature that will enhance investigation, reporting, and discussion of breast implant-associated B-cell malignancies.

Declaration of competing of interest

The authors declare that there are no conflicts of interest regarding the publication of this article, and there have been no significant financial contributions for this work that could have influenced its outcome.

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