

Understanding rare adverse sequelae of breast implants: anaplastic large-cell lymphoma, late seromas, and double capsules

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Abstract: Breast implant-associated anaplastic large cell lymphoma (BI-ALCL) is a distinct type of T-cell lymphoma arising around breast implants. The United States FDA recently updated the 2011 safety communication, warning that women with breast implants may have a very low risk of developing ALCL adjacent to a breast implant. According to the World Health Organization, BI-LCL is not a breast cancer or cancer of the breast tissue; it is a lymphoma, a cancer of immune cells. BI-ALCL is highly curable in the majority of patients. Informed consent should include the risk of BI-ALCL with breast implant patients. Women with breast implants are encouraged to contact their plastic surgeon if they notice swelling, fluid collections, or unexpected changes in breast shape. Physicians are encouraged to send suspicious peri-prosthetic fluid for CD30 immunohistochemistry, cell block cytology, and culture in symptomatic patients. An observation from reported cases indicates a predominance of textured device involvement. More information is needed to fully understand risk factors and etiology. The association of bacteria and biofilm with ALCL is currently being investigated and one theory is that biofilm may play a role in this disease process stressing the importance of best practice techniques intraoperatively. Recent studies have reported clinical presentation, prognosis, and treatment outcomes with long term followup demonstrating the critical role for surgical management.

Keywords: Breast implant-associated anaplastic large cell lymphoma (BI-LCL); anaplastic large cell lymphoma (ALCL); non-Hodgkin lymphoma; CD30; double capsule; late seroma

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Breast implant-associated anaplastic large cell lymphoma (BI-ALCL) background

Over 1.5 million women worldwide receive breast implants annually (1). According to the United States Food and Drug Administration, breast implants have a “reasonable assurance of safety and efficacy”, but are not without

possible short and long-term complications such as infection, device failure, and capsular contracture (2). Breast implant-associated anaplastic large cell lymphoma (BI-LCL) is a very rare T-cell lymphoma that can arise around breast implants placed either for reconstructive or cosmetic indications. While theories have been postulated on the

potential etiology of BI-ALCL, pathogenesis has not yet been clearly defined. Other rare breast implant associations include benign delayed seromas and double capsules, which have been the focus of implant marketing campaigns, but remain poorly understood or described outside of case reports. The purpose of this article is to perform a literature review on the etiology and sequelae of BI-ALCL, benign delayed seromas, and double capsules surrounding breast prostheses.

In 2016, the US FDA updated its 2011 safety communication cautioning about BI-ALCL and included clinical presentation, prognosis, and treatment options (3). The FDA is now aware of 258 adverse event reports of BI-ALCL, however due to the rarity of the disease, the FDA recommended no specific changes to clinical practice for asymptomatic patients with breast implants. Since the FDA safety communication, a number of major worldwide government authorities have developed BI-ALCL patient and physician recommendations. The National Comprehensive Cancer Network (NCCN) released statements on BI-ALCL in 2012, and is expected to issue treatment guidelines in 2017 (4). In response to public concern and published cases, the World Health Organization (WHO) in March 2016 provisionally classified BI-ALCL as a distinct lymphoma with disease-specific surgical treatment recommendations (5). The revision refines diagnostic criteria and emphasizes the importance of surgical management for disease confined to the capsule. The International Agency for Research on Cancer (IARC) in 2014 designated BI-ALCL a priority of further research to determine malignancy etiology and mechanism of pathogenesis (6). In 2015, the US National Cancer Institute (NCI) posted specific surgical recommendations for the treatment of BI-ALCL (7). In 2015, the French National Cancer Institute (Agence Nationale de Sécurité du Médicament, ANSM) released diagnosis and treatment recommendations for BI-ALCL and mandated that all breast implants carry a warning that a clearly established link exists between breast implants and ALCL (8). In July 2016, the ANSM released an update on BI-ALCL based upon their 29 cases and because of a predominance of textured cases, ANSM is calling for all implant manufacturers selling in France to submit clear safety data for textured implants within the year or their respective devices will be restricted from sale (9).

Family of ALCL diseases

Lymphoma is a cancer of the immune system developing

from lymphocytes and is the most common malignancy of the blood (10). Lymphoma broadly includes Hodgkin's lymphoma, Non-Hodgkin's lymphoma (NHL), and a variety of lymphoproliferative disorders. In the United States, approximately 71,850 cases of NHL were diagnosed in 2014 (11). Estimated incidence of T-cell NHL diagnoses in the United States in 2014 was 17,302 (11), which included 1982 cases of ALCL of any type (12). Clinicopathologic subtypes of ALCL range from the more aggressive systemic ALCL down to the indolent CD30 positive lymphoproliferative disorders of the skin that includes a benign lymphomatoid papulosis and the relatively indolent primary cutaneous ALCL (5-yr OS >90% to 95%, lymph node metastases 5%) (13). Multiple sites of disease, frequent lymphadenopathy, and wide dissemination characterize systemic ALCL. Systemic ALCL is further classified by either the expression or absence of the anaplastic lymphoma kinase (ALK) tyrosine kinase receptor gene translocation. ALK+ ALCL accounts for approximately 50 to 80 percent of all ALCLs, and occurs most commonly in males (male/female ratio: 6.5:1) under the age of thirty, and has a 5-yr overall survival (OS) of 70% (5). In contrast, systemic ALK-ALCL is an immunophenotypically and cytogenetically heterogeneous group, and has a 5-year OS 31%. Standard first line chemotherapy is cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP) (14). When treated with chemotherapy, ALK+ ALCL has a higher overall 5-year survival rate than systemic ALK-ALCL (58% versus 34%, respectively) (15,16). As a percentage of all T-cell lymphomas, ALK+ ALCL is more common in North America than Europe or Asia (16.0% vs. 6.4% vs. 3.2%, respectively). Systemic ALK-ALCL is more common in Europe than North America or Asia (9.4% vs. 7.8% vs. 2.6%, respectively) (17).

Overview of BI-ALCL

BI-ALCL is distinct from primary breast lymphoma (PBL), which is a disease of the breast parenchyma, and is predominantly a B-cell lymphoma (65–90%) (18,19), while BI-ALCL is purely a T-cell lymphoma arising either in an effusion surrounding the implant or in the scar capsule surrounding a breast implant (20,21). All confirmed reported cases of BI-ALCL are ALK—and express the CD30 cell surface protein (*Table 1, Figure 1*). Most cases are diagnosed during implant revision surgery performed for a late onset (>1 year), persistent seroma and may be associated with symptoms of pain, breast lumps, swelling, or

Table 1 Criteria for diagnosis of breast implant-associated anaplastic large cell lymphoma

A tumor with adequate pathological specimen for analysis, involving an effusion either surrounding a breast implant lining a breast implant capsule
Neoplasm with large lymphoid cells with abundant cytoplasm and pleomorphic nuclei
Tumor demonstrates T-cell markers with uniform expression of CD30 by immunohistochemistry or flow cytometry
Negative for anaplastic lymphoma kinase (ALK) protein or translocations involving the <i>ALK</i> gene at chromosome 2q23

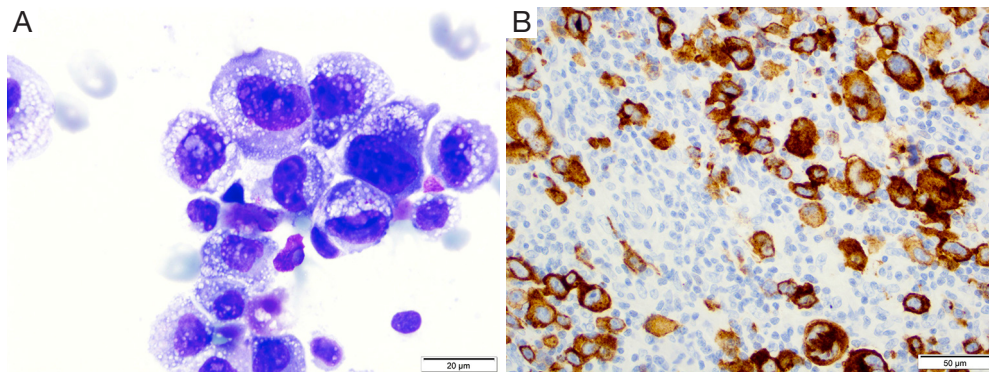


Figure 1 BI-ALCL histology. (A) Wright Giemsa staining from a malignant effusion of BI-ALCL demonstrating pleomorphic cells with horseshoe shaped nuclei, nuclear folding and abundant vacuolated cytoplasm (1,000× magnification); (B) immunohistochemistry in tissue section demonstrates sheets of large cells positive for CD30 in a case of BI-ALCL. BI-ALCL, breast implant-associated anaplastic large-cell lymphoma. (Reprinted with permission from Clemens MW, Miranda RN. Coming of Age: Breast Implant-Associated Anaplastic Large Cell Lymphoma After 18 Years of Investigation. *Clin Plast Surg* 2015;42:605-13.)

breast asymmetry. The number of BI-ALCL cases reported in primary augmentation and reconstruction for breast cancer or prophylaxis are nearly equivalent. BI-ALCL most commonly follows an indolent course provided adequate surgical ablation of the implant and surrounding capsule without systemic therapy, but aggressive exceptions, disease progression, and death have been reported (22).

Etiology of BI-ALCL

No risk factors have been clearly identified for ALCL though many have been theorized including the presence of a subclinical biofilm, response to particulate from textured implants, a consequence of capsular contracture or repeated capsular trauma, and/or genetic predisposition but these observations have not been confirmed in formal epidemiological studies (23). Recent studies have demonstrated a possible pathogenic mechanism of chronic T-cell stimulation with local antigenic drive, ultimately leading to the development of lymphoma (24). The immune system's response to chronic inflammation surrounding the

breast implant in a genetically susceptible patient, may lead to genetic degeneration and dysplasia (25). In a recent study by Hu *et al.*, the authors compared the implant capsules of patients with BI-ALCL to those with normal capsular contracture, finding a high bacterial load and significantly different microbiome in the BI-ALCL specimens with a high predominance of the bacteria *Ralstonia pickettii*, a gram-negative rod and common contaminant of drinking water (26). Previous work comparing the capsules of textured and smooth implants in pigs showed that there are increased lymphocytes on textured breast implants, with a T-cell predominance, further supporting texturing as a link to chronic inflammation and T-cell response. Kadin and colleagues demonstrated that patterns of cytokine and transcription factor expression such as *SOCS3*, *JunB*, *SATB1* are suggestive of a Th1 phenotype which further supports the theory that BI-ALCL may arise from chronic bacterial antigen stimulation of T-cells (27). Further research is required to identify modifiable risk factors and susceptible populations, however based upon these preliminary findings, standard of care sterility technique

such as antibiotic prophylaxis and no-touch practice remains prudent when placing a breast implant (28).

Epidemiology of BI-ALCL

Since 1997, approximately 136 patients have been reported in case reports of BI-ALCL (29-53). A number of epidemiologic studies have failed to show an association between breast augmentation and risk of lymphoma, however these studies were limited by the number of patients enrolled or by the insufficient time period of follow up (54-56). These studies underscore the difficulty of determining the incidence and prevalence of a very rare and recently recognized clinical entity. Large prospective outcomes studies of textured implants are rare. McGuire and colleagues reported four patients with BI-ALCL occurring in a prospective cohort of 17,656 patients with textured implants at a mean follow up of 3.4 years (57). de Jong and colleagues reported an individually matched case control study from the Netherlands nationwide pathology database (58). The authors found a positive association for the development of ALCL in women with breast implants compared to those without an implant with an odds ratio of 18.2 (95% confidence interval, 2.1–156.8). Based upon these data, the authors estimated an incidence of 0.1 to 0.3 per 100,000 BI-ALCL cases for women with prostheses per year. Another way of representing these numbers is that 1 in 500,000 women are at risk of developing the disease after 1 year. However, the disease on average occurs at 10 years and therefore at that time point, 1 in 50,000 women with breast implants are at risk of developing the disease.

Presentation and diagnosis of BI-ALCL

Two-thirds of BI-ALCL patients will present as a malignant effusion associated with the fibrous capsule surrounding an implant occurring on average 8 to 10 years after implantation. Any seroma occurring greater than 1 year after implantation not readily explainable by infection or trauma should be considered suspicious for disease (*Figure 2*). One third of patients present with a mass which may indicate a more aggressive clinical course. Adrada and colleagues reviewed 44 BI-ALCL patients with imaging studies and reported on the sensitivity/specificity for detecting an effusion using ultrasound (84%/75%), computerized tomography (55%/83%), magnetic resonance imaging (82%/33%), and positron emission tomography

(38%/83%) (59). Additionally, the sensitivity/specificity to detect a BI-ALCL mass was reported for ultrasound (46%/100%), computerized tomography (50%/100%), magnetic resonance imaging (82%/33%), and positron emission tomography (64%/88%). The sensitivity of mammography was found to be inferior for BI-ALCL effusion and mass. Ultrasound is utilized at our institution as a screening tool for suspected cases and in combination with PET for confirmed cases to determine extension and for surveillance of disease (*Figure 2*).

For suspected patients, any aspiration of periprosthetic fluid should be sent to pathology for cytologic evaluation and include a clinical history with the stated intent to “rule out BI-ALCL”. Pathologic evaluation may demonstrate BI-ALCL as individual cells, cell clusters in aggregates, or as cohesive sheets. Diagnosis using Wright-Giemsa or hematoxylin and eosin staining alone is usually insufficient, however BI-ALCL will demonstrate strong and uniform membranous expression of CD30 immunohistochemistry. Ultrasound may help define the extent of an effusion, and can be helpful in identifying any associated capsule masses. Clinical examination should include evaluation of regional lymph nodes. Volumes of an effusion can range from 50 to 1,000 mL and is typically more viscous than a benign seroma owing to the high protein content and cellularity. The surrounding capsule may be thickened and fibrous or may be deceptively unremarkable on gross examination consistent with the under appreciation of this lymphoma. If a mass is present, it can protrude into the implant creating a mass effect distortion on imaging, or the mass may protrude outward into the soft tissue.

Treatment and staging of BI-ALCL

Patients with biopsy-proven BI-ALCL must be referred to a lymphoma oncologist ideally prior to any surgical intervention to allow for proper oncologic evaluation. Surgical treatment of BI-ALCL requires complete tumor ablation, which includes removal of the implant, complete removal of any disease mass with negative margins, and total capsulectomy. Because an implant capsule may drain to multiple regional lymph node basins, there does not appear to be a role for sentinel lymph node biopsy in the treatment of BI-ALCL. Fine needle aspiration of enlarged lymph nodes can yield a false negative and therefore excisional biopsies should be performed of any suspicious lymph nodes. The involvement of a surgical oncologist in the management of this lymphoma is recommended. An

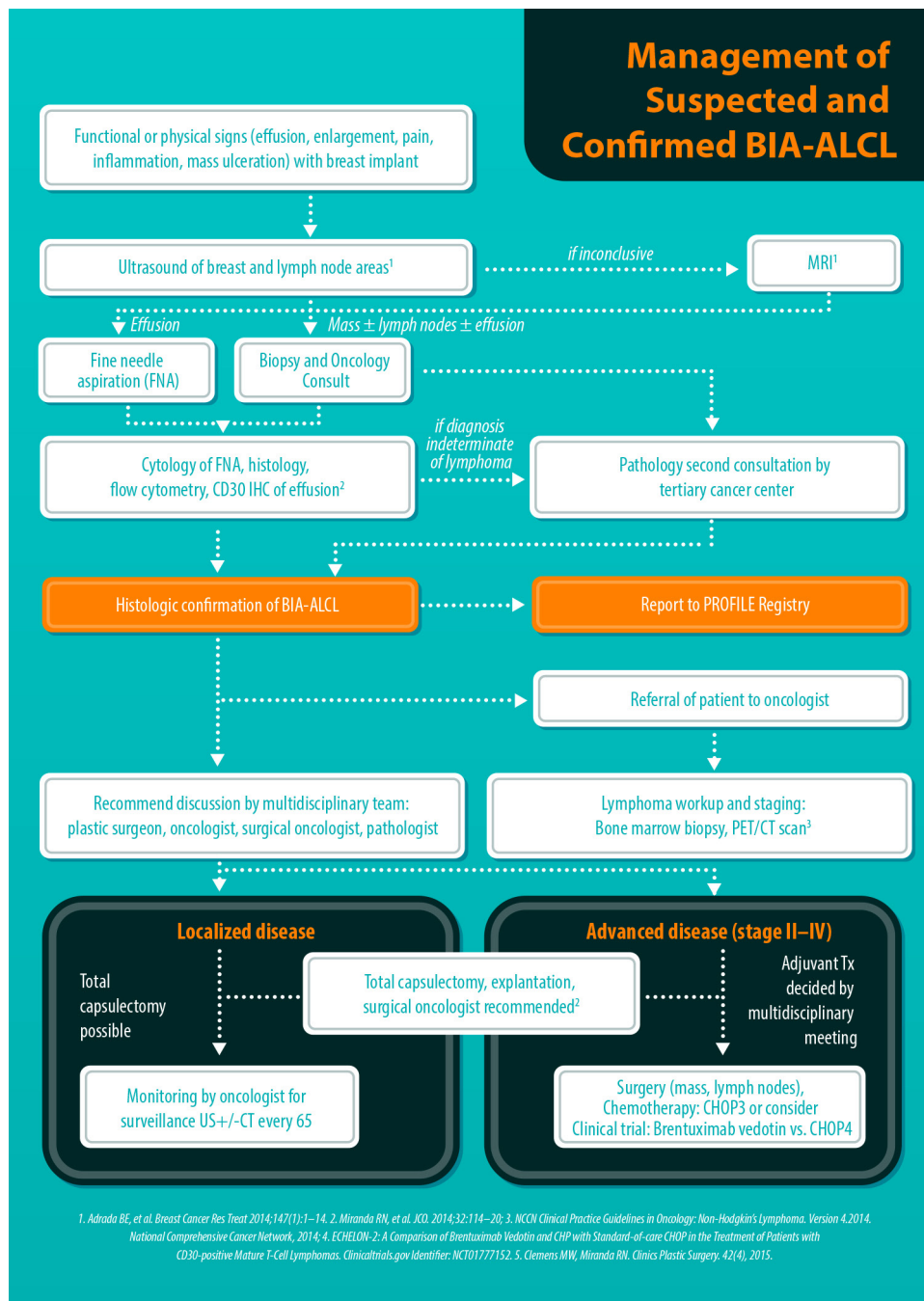


Figure 2 Algorithmic approach to a patient with a delayed seroma and suspected BI-ALCL. This algorithm was developed at MD Anderson and subsequently adopted by the American Society of Plastic Surgeons (ASPS) and the American Society of Aesthetic Plastic Surgery (ASAPS). BI-ALCL, breast implant-associated anaplastic large-cell lymphoma. [Reprinted with permission from Clemens MW, Butler CE. ASPS/PSF Efforts on BIA-ALCL. Plastic Surgery News 2015;26(7).]

incomplete resection or inadequate local surgical control may subject the patient recurrence, or to the need for adjunctive treatments such as chemotherapy and radiation

therapy whereas complete resection may be the definitive treatment in the majority of cases. Surgery should be performed with strict oncologic technique including use

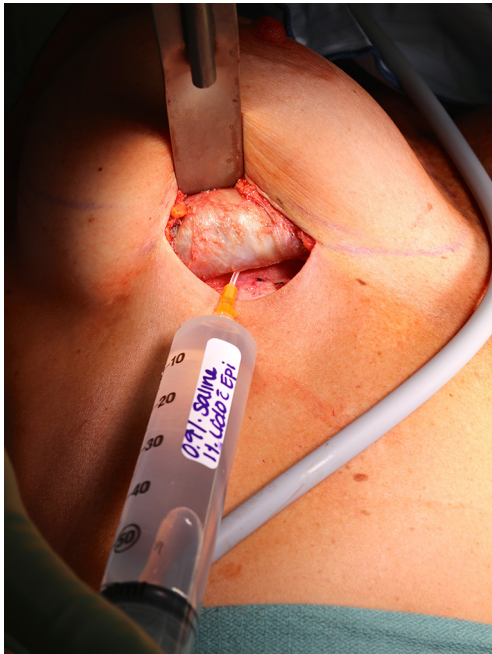


Figure 3 Complete capsulectomy. Treatment of BI-ALCL includes total capsulectomy with excision of any associated masses as residual disease left on the chest wall may continue to progress and require further treatment such as chemotherapy. With subpectoral implants, elevation of the posterior capsular wall off of the rib cage may be difficult but is still essential. Pictured is standard tumescence being infiltrated by angiocath into the posterior capsule of a BI-ALCL patient to facilitate complete removal of the capsules. BI-ALCL, breast implant-associated anaplastic large-cell lymphoma.

of specimen orientation sutures placement of surgical clips within the tumor bed, and use of new instruments if performing a contralateral explantation (*Figure 3*). At this time, the FDA does not recommend screening or prophylactic implant removal for asymptomatic patients or patients with familial susceptibility cancer. All implant patients can have a minute amount of periprosthetic fluid which is normal and does not require screening (*Figure 4*). Although reimplantation with a textured implant is not recommended, several BI-ALCL patients have received implant replacement with a smooth implant following definitive treatment, and these patients are being closely monitored for any disease recurrence.

Patients with BI-ALCL or any type of lymphoma are traditionally staged by the 1971 Ann Arbor Classification which stages disease based upon progression as a “liquid tumor” (60). Under this classification, nearly all BI-ALCL

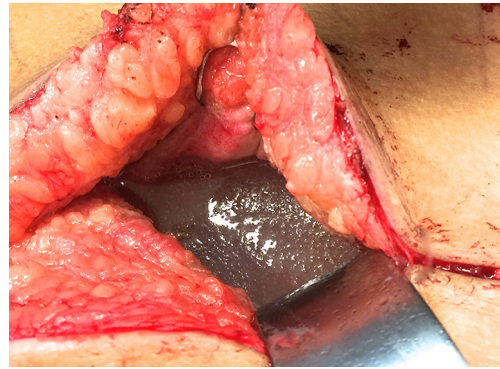


Figure 4 Normal periprosthetic fluid. All breast implant patients can have a minute amount of periprosthetic fluid which is normal. Small collections of fluid incidentally found on imaging or at an implant exchange in an asymptomatic patient do not require screening with CD30 immunohistochemistry.

patients fall under one of two stages, either stage 1E (84%) or stage IIE (16%). Although most patients with BI-ALCL have a relatively indolent clinical course, reports of deaths attributable to disease emphasize the importance of a timely diagnosis and adequate treatment with appropriate surveillance or else disease progression can occur with detrimental effect. Patients with BI-ALCL who have died were described with local or regional extension of their disease, and very rare distant organ metastasis. This pattern of progression suggests that BI-ALCL is a distinct entity, and displays progression more similar to solid tumors than to other non-Hodgkin lymphomas. This pattern of disease spread is also better suited to a clinical and pathologic staging system modeled after the American Joint Committee on Cancer (AJCC) TNM (Tumor, Lymph node, Metastasis) system for staging solid tumors (61). A recent MD Anderson BI-ALCL TNM staging system seems to be more applicable than the Ann Arbor system for predicting prognosis and for evaluating treatment regimens in patients with BI-ALCL (62) (*Figure 5, Table 2*).

Clinical characteristics and BI-ALCL outcomes

The clinico-pathologic features of BI-ALCL have been reported in several literature reviews. In 2014, Miranda *et al.* reviewed the long-term follow up of 60 BI-ALCL patients (52). The mean age was 52 years old (range, 28 to 87 years) with a median of 9 years (range, 1 to 32 years) between implantation and lymphoma diagnosis. Patients presented with either a malignant effusion improperly

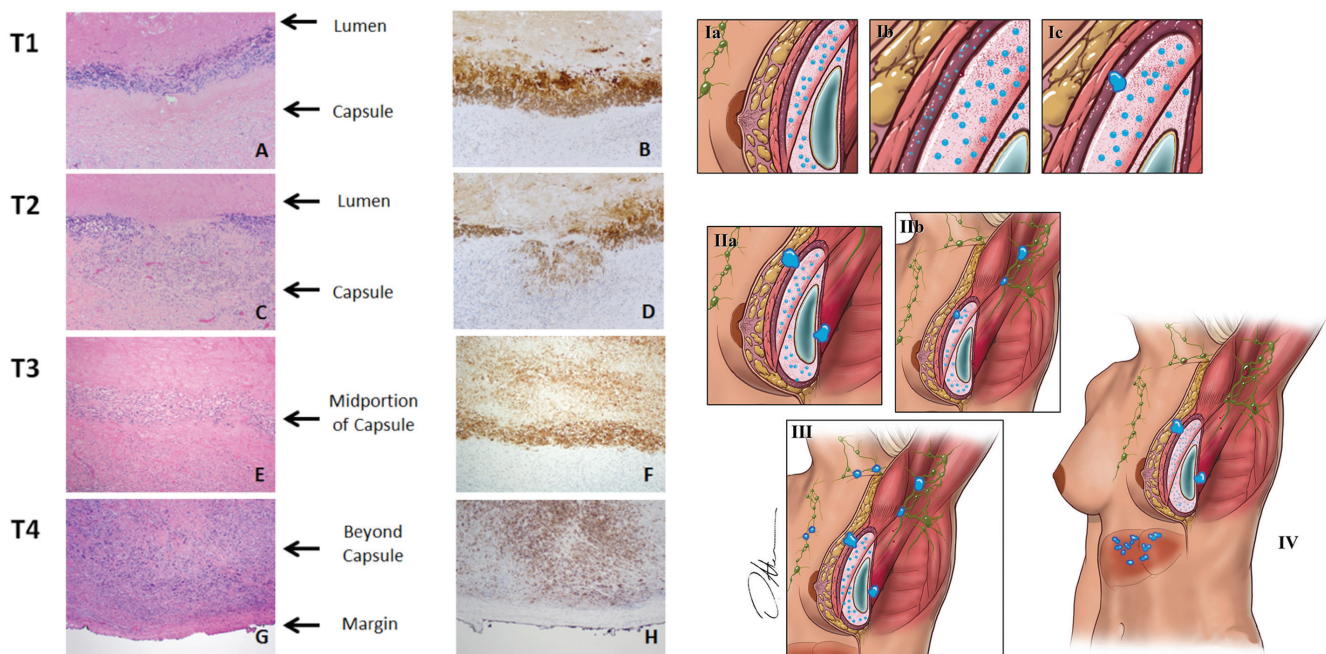


Figure 5 BI-ALCL staging system: this TNM system was modeled after the American Joint Committee on Cancer (AJCC) TNM (tumor, lymph node, metastasis) staging system for solid tumors. T1: lymphoma cells confined to the effusion or a layer on the luminal side of the capsule (IA); T2: lymphoma cells superficially infiltrate the luminal side of the capsule (IB); T3: clusters or sheets of lymphoma cells infiltrate into the thickness of the capsule (IC); and T4: lymphoma cells infiltrating beyond the capsule (IIA), into the adjacent soft tissue or breast parenchyma (III, IV). ($\times 100$). (Reprinted with permission from Clemens MW, Medeiros LJ, Butler CE, *et al.* Complete Surgical Excision Is Essential for the Management of Patients With Breast Implant-Associated Anaplastic Large-Cell Lymphoma. *J Clin Oncol* 2016;34:160-8.)

called seroma (70%) or a distinct mass (30%). The median overall survival (OS) was 12 years (median follow-up, 2 years; range, 0–14 years). A total capsulectomy with implant removal was performed in 93% of patients. OS and progression free survival (PFS) were similar between patients who received and did not receive chemotherapy ($P=0.44$ and $P=0.28$, respectively), suggesting that some patients may achieve optimal outcomes with an adequate surgical approach (Figure 6). Radiation therapy has also been used for local control of disease, and further research is required to determine specific indications for adjunctive treatments. Patients with a breast mass had a worse OS and PFS ($P=0.052$ and $P=0.03$, respectively). At this time, it is unclear whether the association of mass and worse prognosis indicates a more aggressive variant, more progressed disease, or perhaps a consequence of inadequate surgical ablation of tumor infiltration. Event free survival and overall survival by different treatment modalities are summarized in Figure 7.

Hart *et al.* performed a meta-analysis and identified 53

BI-ALCL patients (63). For patients with available clinical data, the authors noted rates of 17.3% extracapsular disease and 23.1% with the presence of a mass. 39.6% of patients were treated with surgery alone, 9.4% with surgery and radiation, 18.9% with surgery and chemotherapy, 30.2% with surgery, chemotherapy, and radiation, and 1.9% with chemotherapy alone. At a median follow up of 15 months (range, 3.6–90 months), disease recurrence was 28.3%, of which 73.3% were treated with salvage chemotherapy. BI-ALCL was attributed to four patient deaths. Extracapsular disease extension was associated with increased risk for recurrence ($P<0.0001$) and patient death ($P=0.0008$). This study also found a statistically significant difference in three and 5-year survival rates between patients presenting with and without a mass ($P=0.0308$ and $P=0.0308$, respectively). While BI-ALCL may follow a relatively indolent course in most patients, reports of disseminated cancer and deaths attributed to the disease emphasizes the importance of timely diagnosis and adequate treatment with appropriate surveillance.

Table 2 Clinicopathologic features of patients with breast implant-associated anaplastic large-cell lymphoma

Clinical feature	Patients with BI-ALCL
Age, years	
Median	54
Range	28–87
Laterality	
Right	46 (52.9)
Left	37 (42.5)
Bilateral	4 (4.6)
Reason for initial implantation	
Cosmetic	51 (58.6)
Breast cancer reconstruction	36 (41.4)
Type of implant (n=81)	
Silicone	40 (49.4)
Saline	41 (50.6)
Texture of implant (n=48)	
Purely textured	45 (93.7)
Purely smooth	0 (0)
Both smooth/textured	3 (2.3)
Interval to lymphoma diagnosis, years	
Median	8
Mean	9.1
Range	2–25
Clinical presentation	
Effusion only	52 (59.8)
Mass only	15 (17.2)
Effusion and mass	17 (19.5)
No mass, no effusion	3 (3.4)
T stage	
T1	31 (35.6)
T2	11 (12.6)
T3	14 (16.1)
T4	30 (34.5)
N stage	
0	74 (85.1)
1	13 (14.9)

Table 2 (continued)**Table 2** (continued)

Clinical feature	Patients with BI-ALCL
Ann Arbor stage at presentation	
IE	74 (86.2)
IIE	13 (13.8)
TNM stage at presentation	
IA	31 (35.6)
IB	10 (11.5)
IC	12 (13.8)
IIA	22 (25.3)
IIB	4 (4.6)
III	8 (9.2)
IV	0 (0)
Chemotherapy (n=51)	
CHOP	44 (86.3)
3 cycles	11
4 cycles	2
6 cycles	28
NA	3
CHOEP	11 (21.6)
6 cycles	11
NS	2 (3.9)
ABVD	2 (3.9)
Hyper-CVAD	1 (1.9)
Follow-up, months	
Median	30
Mean	45
Range	3–217

Data are given as No. (%) unless otherwise noted. Abbreviations: ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; BI-ALCL, breast implant-associated anaplastic large-cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOEP, CHOP plus etoposide; hyper-CVAD course A, hyperfractionated; cyclophosphamide, vincristine, doxorubicin, and dexamethasone with course B: methotrexate and cytarabine; NA, not available; NS, chemotherapy not specified. (Reprinted with permission from Clemens MW, Medeiros LJ, Butler CE, *et al.* Complete Surgical Excision Is Essential for the Management of Patients With Breast Implant-Associated Anaplastic Large-Cell Lymphoma. *J Clin Oncol* 2016;34:160-8.)

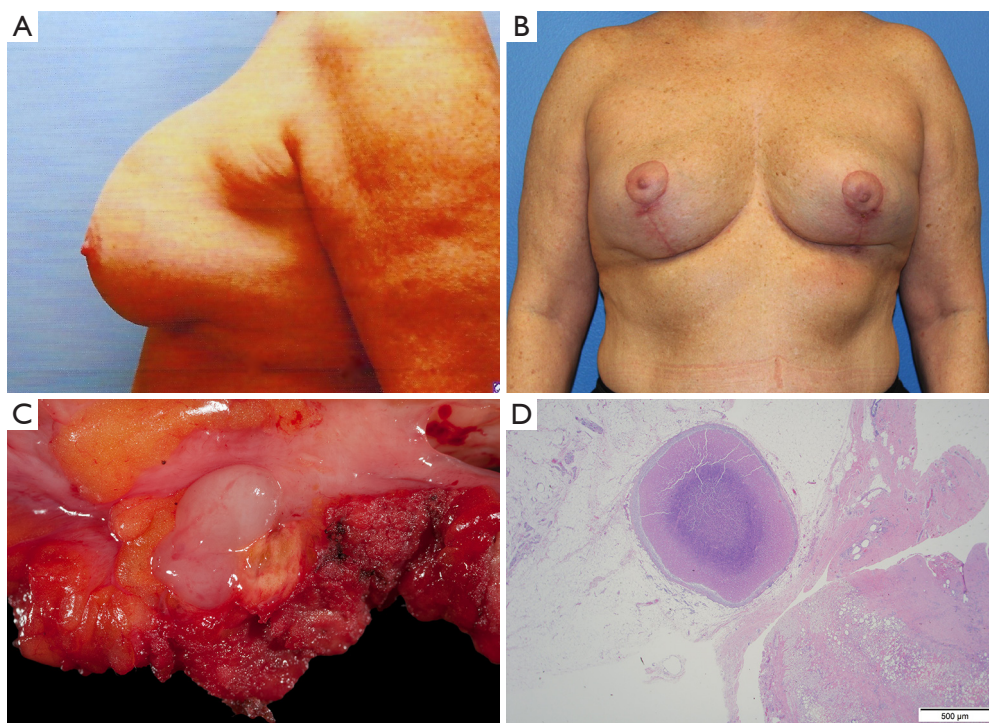


Figure 6 Clinical image of a 52-year-old woman who received a cosmetic breast augmentation with textured silicone implants. Twenty years after implantation, she developed swelling of the left breast of recent onset which was aspirated multiple times. (A) Patient then received a partial capsulectomy, implant removal and mastopexy; (B) adequate tumor resection was questionable and despite being asymptomatic, the patient underwent a completion capsulectomy with excision of the posterior capsular wall; postoperative pathology again demonstrated persistent BI-ALCL disease of her chest wall and now with free margins; (C) tissue section demonstrates a nodule with compact tumor cells. Immunohistochemistry demonstrates that most tumor cells (D) which express CD30. Patient received no further adjunctive treatments and is currently 2 years disease free. BI-ALCL, breast implant-associated anaplastic large-cell lymphoma. (Reprinted with permission from Clemens MW, Miranda RN. Coming of Age: Breast Implant-Associated Anaplastic Large Cell Lymphoma After 18 Years of Investigation. *Clin Plast Surg* 2015;42:605-13.)

Brody and colleagues recently reported a summary of 79 published patients and 94 previously unreported cases (64). The authors report that for all implants where surface characteristics were known, there was at least one textured device used within the patient's surgical history. The authors reconfirm that there are no known pure smooth implant cases and importantly note that BI-ALCL has been reported in association with all major forms of implant texturing techniques from current implant manufacturers. Our institutional experience has been similar and is summarized in *Table 3*. We have noted most patients having slow disease progression and a good prognosis when adequately treated, but conceded occasional lymphadenopathy, metastases, and nine attributable deaths.

Future research is warranted to determine if certain patients have a predisposition to the development of the

disease and if any modifiable risk factors exist either with the patient or type of implant utilized. Advances in the treatment of T cell lymphomas give promise for BI-ALCL refractory to surgical therapy alone. Brentuximab vedotin is a novel anti-CD30 monoclonal antibody that has improved the management of systemic ALCL with a reported objective response rate of 86% and complete remission rate of 59% in relapsed or refractory systemic ALCL in clinical trials (65,66). Prospective trials of BI-ALCL patients at major referral centers may help delineate chemotherapeutic sensitivity and efficacy of novel agents.

Informed consent and reporting

Following recommendations made by the FDA in 2011, implant manufacturers added language warning on the

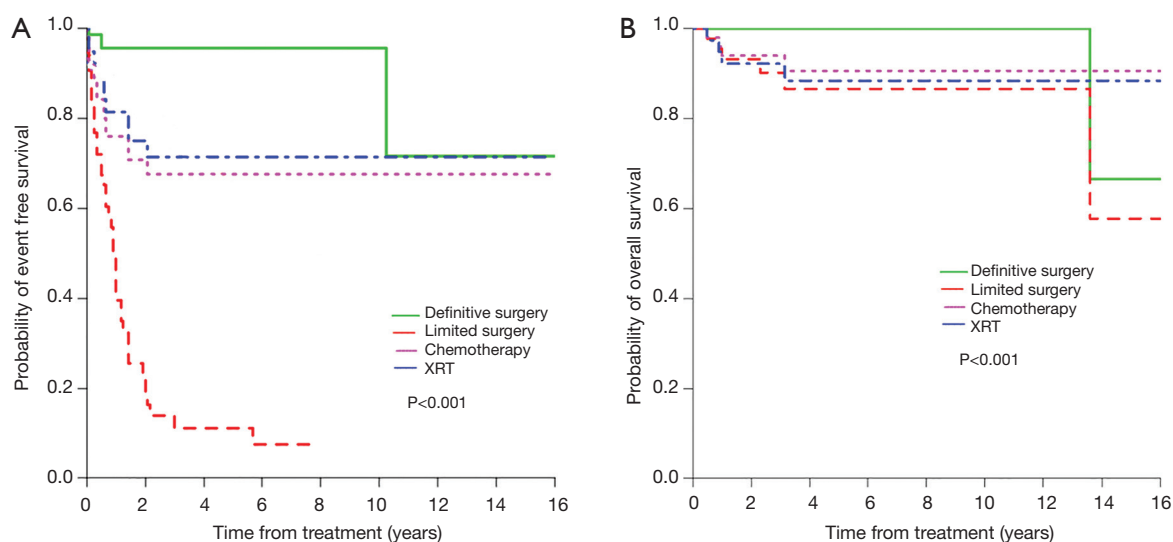


Figure 7 Survival curves according to treatment approaches. Event-free survival (A), overall survival (B). (Reprinted with permission from Clemens MW, Medeiros LJ, Butler CE, *et al.* Complete Surgical Excision Is Essential for the Management of Patients With Breast Implant-Associated Anaplastic Large-Cell Lymphoma. *J Clin Oncol* 2016;34:160-8.)

Table 3 Distribution BI-ALCL patients by Manufacturer. Note MD Anderson and USC reporting are worldwide whereas FDA MAUDE database is predominantly a United States catchment of cases

Institution	Manufacturer	N (%)
Worldwide cases by MD Anderson Tracking 2016	Unknown	87 (47.8)
	Allergan/Inamed/McGhan	76 (41.8)
	Mentor	6 (3.3)
	Nagor	3 (1.7)
	Eurosilicone	1 (0.6)
	PIP	5 (2.8)
	Sientra/Silimed	3 (1.7)
	Bioplasty	1 (0.6)
Worldwide Cases Reported by USC 2015	Unknown	61 (35.0)
	Allergan/Inamed/McGhan	97 (56.0)
	Mentor	3 (1.7)
	Nagor	3 (1.7)
	Eurosilicone	0
US MAUDE Database as of 2015	PIP	5 (2.9)
	Sientra/Silimed	1 (0.5)
	Unknown	22 (9.6)
	Allergan/Inamed/McGhan	184 (80.3)
	Mentor	20 (8.7)
	CUI	1 (0.4)
Sientra	1 (0.4)	

existence of BI-ALCL to breast implant package inserts within the United States and Canada. Breast implant informed consent examples that include the risk of BI-ALCL were subsequently produced by the American Society of Plastic Surgeons (ASPS) and are available for download from the www.plasticsurgery.org website. With respect to BI-ALCL, risk disclosure should have at least three basic objectives (67). The first objective is to make patients aware of the existence of this rare disease. The second objective is for patients to understand common presenting symptoms such as a breast mass or delayed-presentation seroma or effusion. The final objective is to compel patients to take action and follow up with a physician should these symptoms occur. Printed copies of a patient's signed consent as well as procedure specific informational pamphlets at an initial consultation will enable patients to further digest surgical details at their leisure in their own homes, and engenders more effective recall.

Many resources exist for oncologists and surgeons treating a BI-ALCL patient. The Plastic Surgery Foundation paired the American Society of Plastic Surgeons and the US FDA to form the PROFILE registry (Patient Registry and Outcomes For breast Implants and anaplastic large cell Lymphoma etiology and Epidemiology). The FDA specifically recommends the reporting of confirmed cases to the PROFILE registry. The purpose of PROFILE

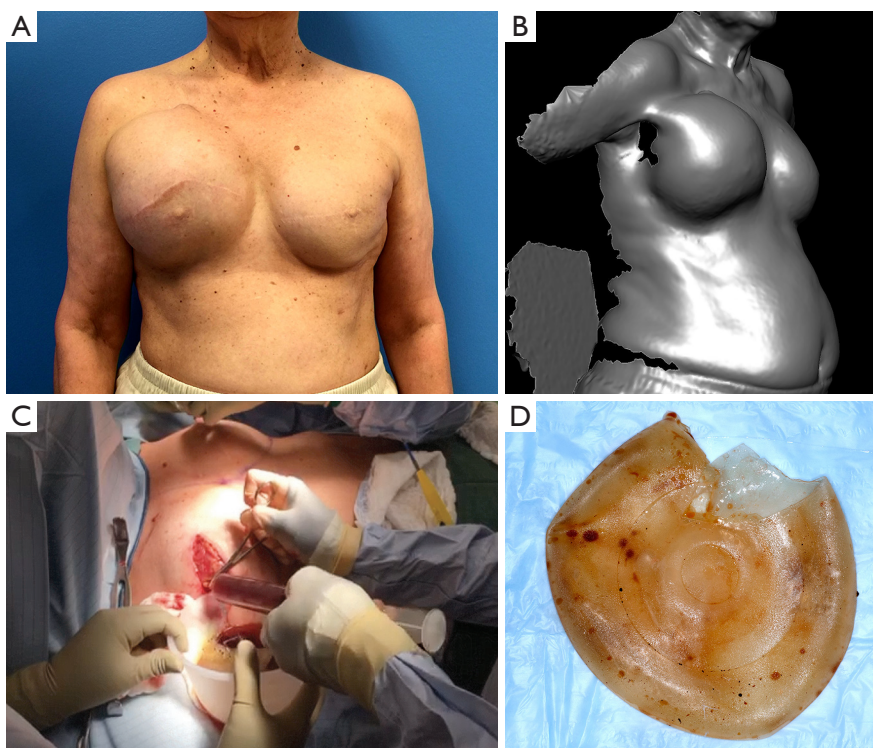


Figure 8 Delayed seroma. A 70-year-old female with history of right breast cancer status post bilateral mastectomy and Mentor textured implant reconstruction in 1992. Twenty-four years post implantation, patient developed a delayed seroma of the right breast. (preoperative A, 3-D imaging topography view B, intraoperative drainage C). Breast implant had no manufacturer markings but was confirmed based on review of original operative notes as well as negative imprint stamp texturing observed on implant. (explant D) Following total capsulectomy and implant exchange, patient had no further fluid collections or complications.

is to increase the scientific data on BI-ALCL in women with breast implants as well as to support research to characterize BI-ALCL and to elucidate the exact role of breast implants in the etiology of the disease. In addition to providing plastic surgeons, oncologists, and patients with information they need about breast implants and treatment of BI-ALCL, confirmed cases in the registry will be available for analytical epidemiological studies. Treating physicians are encouraged to report confirmed cases to the PROFILE website which can be found at www.thepsf.org.

Benign delayed seromas

Benign delayed seromas are collections of serous fluid spontaneously occurring around a prosthesis more than 1 year after implantation. While delayed fluid collections are the most common presenting symptom for BI-ALCL patients, the mechanism is completely different as BI-

ALCL develops a true malignant effusion due to the high protein content and cellularity of the fluid as well as the effect of interleukin production by the anaplastic cells resulting in local vascular leakage. It is important to differentiate these two distinct unrelated processes as there is a common misperception that they are on a continuum with one leading into the other. Benign fluid collections are not precursors to the development of BI-ALCL, and to date there has not been reported a patient with recurrent benign seromas that then converted to a CD30 positive effusion.

Benign late seromas most commonly follow blunt external trauma (i.e., Motor vehicle accident, closed capsulectomy) or low grade infection, however they can also occur in the absence of any discernible precipitating event (68-70) (*Figure 8*). Spear and colleagues reported a 5-year experience of 28 late seromas encountered in 25 patients (71). The authors found that 96 percent had a Biocell (Allergan) textured device in place at the time of seroma development.

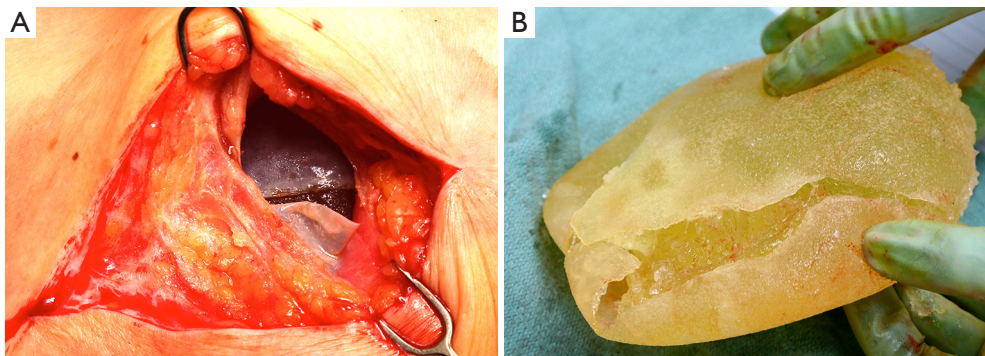


Figure 9 “Double capsule”. A 56-year-old female developed contour deformity of her reconstructed breast following blunt trauma to the chest in a motor vehicle accident. Patient delayed in addressing the deformity for 1 year. At explantation, multiple capsules were encountered (A) over the ruptured implant (B).

The authors did note that within the surgical practices reviewed, 51% of patients received a smooth implant and 49% of patients received a Biocell textured implant, the only type of texturing utilized by the authors. This finding points to delayed seromas being primarily though not exclusively a textured implant sequelae. The late seromas in the series were managed with 53.6% complete capsulectomy, seroma drainage, and new implant exchange, 10.7% by seroma drainage and implant exchange, 7.1% by complete capsulectomy/seroma drainage with no implant replacement, 17.9% by only seroma aspiration alone, and 10.7% by antibiotic therapy alone. While all cultures were negative, it's important to note that advanced biofilm detection techniques such as PCR pyrosequencing and scanning electron microscopy were not employed nor was routine CD30 immunohistochemistry testing to rule out BI-ALCL. It is recommended to test all delayed seromas not readily explainable with CD30 immunohistochemistry.

Maxwell and colleagues reported on the 10-year Core data of Allergan's 410 implant in 941 patients and found a delayed seroma rate of 0.6% (72). The overwhelming majority of late seromas reported in case reports appear to be idiopathic. In a prospective multicenter trial of 17,656 textured implant patients, McGuire and colleagues reported delayed seromas occurring in 26 of 17,656 subjects (0.15%) and 31 of 31,992 implanted devices (0.10%) (57). These late onset seroma rates are similar to those reported for smooth devices, and therefore texturing has not demonstrated an incremental risk of late seroma relative to other implants. Mazzocchi theorized that possible friction irritation from either a fold in the device or rubbing of a textured implant may be responsible in a minority of delayed

seromas (73). A graduated management approach from conservative aspiration progressing to complete capsulectomy will eradicate the vast majority of delayed seromas. Considering many BI-ALCL patients have disease confined to the capsule, it is possible that some patients prior to widespread recognition of the disease were treated with capsulectomy without ever receiving a diagnosis. However, a blind approach is less than optimal when managing a malignancy.

Double capsules

Nearly all synthetic implantable devices including breast implants will form some varying degree of scar encapsulation composed of disorganized collagen and fibroblasts. The observation of double capsules has been described in limited series and case reports predominantly in textured implants (*Figure 9*). Findlay reported her experience of 14 patients with observed double capsules (74). All occurred in textured implants and specifically with Biocell texturing though Dr. Findlay did not report what type of texturing she prefers for augmentation mammoplasty in general. 50% of the patients were asymptomatic and were incidentally found to have double capsules during revisionary surgery. Five of the patients had capsular contracture though extra capsules do not seem to automatically lead to capsular contraction. A postulated theory of double capsules is that the initial adherence of a capsule to a textured implant surface becomes separated with minor trauma tearing away from the old capsule and developing a new capsule. The resulting rough surfaces may create a seroma in between the capsule planes because of shear forces. Smooth implants may not be as susceptible to reinjury phenomena just as polyurethane

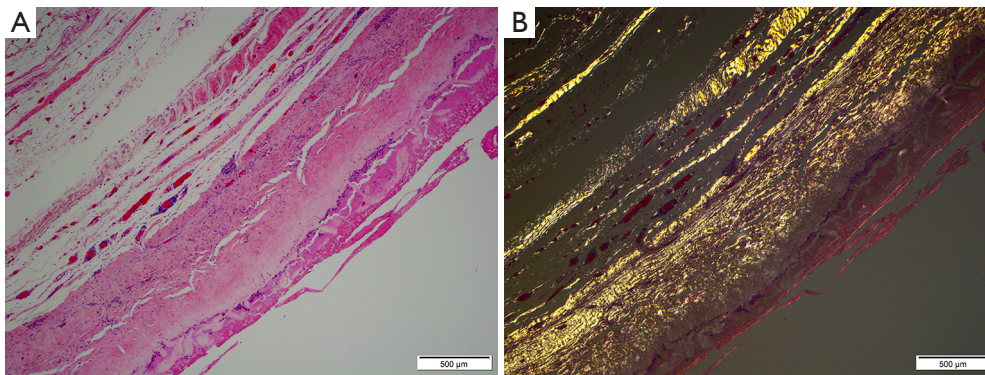


Figure 10 “Double capsule” histology. Haematoxylin and eosin staining of a breast implant capsule (A) and tissue polarization on birefringent lens (B) demonstrates laminar deposition of multiple layers of capsules having developed over two decades.

implants, because of a more robust tissue ingrowth of the capsule, are also less prone to these sequelae of implants. Anecdotally, we have seen double capsules as well as triple and quadruple capsules around textured breast implants (Figure 10). Collagen fibers exhibit a laminar deposition, sometimes demonstrating the characteristic imprint of the texture surface in between layers of the capsule likely representing an original capsule that either tore or lifted away due to a subclinical biofilm on the surface of the implant. The exact etiology of double capsules is unclear and likely multifactorial. The clinical consequence of a double capsule may be a delayed seroma, capsular contracture, or may be a nonentity as many patients are completely asymptomatic.

Conclusions

Unusual sequelae of breast implants such as BI-ALCL, benign delayed seromas, and double capsules remain rare. BI-ALCL is a rare lymphoma associated with breast implants though the exact etiology and pathogenesis remain unclear. Timely diagnosis of BI-ALCL and differentiation from benign seromas is dependent on appropriate testing with CD30 immunohistochemistry. The majority of BI-ALCL patients demonstrate a good prognosis with adequate surgical treatment. Textured implants are most commonly implicated in the development of these rare associations, and further research is critical for identification of risk factors and prevention of future cases.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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