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Clinical Implications and Management of Non-ALCL Breast Implant Capsular Pathology

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SUMMARY

The breast implant capsule is a dynamic structure that forms following the implantation of a device. Although normally benign, increased awareness of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) highlights that disease may arise from the capsule. BIA-ALCL presents as a late seroma or mass but explains few of the late seromas found in breast implant patients. To date, many of these seromas lack a clear etiology and are often described as "idiopathic." Several benign and malignant breast implant capsular pathologies can cause a late seroma or mass. Similar to early reports of BIA-ALCL, these conditions are rare and largely limited to case reports or series.

The purpose of this special topic is to present a narrative review highlighting capsular pathologies that contribute to the formation of late seroma or mass in an attempt to broaden the differential diagnosis and help plastic surgeons identify the etiology. Specifically, we review the presentation and management of BIA-ALCL, synovial metaplasia, capsular epithelialization, late hematoma, double capsule, breast cancer, squamous cell carcinoma, mesenchymal tumor, and B-cell lymphoma. Although rare, plastic surgeons should consider these capsular conditions as causes of late seromas and masses. Usually, these conditions may be diagnosed by following the National Comprehensive Cancer Network (NCCN) screening guidelines for BIA-ALCL. Thorough evaluation and workup of late seromas and masses may lead to improved characterization of these rare breast implant capsular conditions and improve our understanding of their pathophysiology and management.

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INTRODUCTION

Breast implant capsular pathology has gained increased attention among plastic surgeons because of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). While BIA-ALCL dominates the discussion on pathologies associated with the breast implant capsule, there are other benign and malignant capsular conditions involving the breast implant capsule that warrant consideration by plastic surgeons treating patients with a late seroma or capsular mass.

The breast implant capsule forms via a foreign body reaction to the implant. Immediately after implant placement, capsule formation begins with coagulation and accumulation of cellular debris and progresses through protein adsorption, acute inflammation, chronic inflammation, and fibrous encapsulation.[1] The breast implant capsule contains three layers: 1) an inner layer of fibroblasts and macrophages, 2) an intermediate layer of loose connective tissue fibrils rich in vasculature, and 3) a dense, vascular, outer collagen layer.[2] Capsular evolution occurs in response to several factors, such as implant texture, infection or biofilm, and radiation.[3] While most capsules remain benign, some undergo varying degrees of fibrosis and/or develop a seroma or mass.[4]

A seroma is defined as “late” if it occurs more than 1 year after implantation.[5] One to two percent of breast implant placements result in late seroma; most are associated with textured implants.[6–8] While plastic surgeons routinely screen for BIA-ALCL when encountering late periprosthetic fluid collection, most late seromas occur due to conditions and capsular pathologies other than BIA-ALCL. DiNapoli reported that only 9% of late seromas in breast implant patients were positive for BIA-ALCL.[4] A more recent study on magnetic resonance imaging (MRI) to screen for silent rupture found that 1.7% of patients had periprosthetic fluid collection; 14 out of 15 were benign and only one was positive for BIA-ALCL.[9]

The rapid accumulation of data on BIA-ALCL has, quite appropriately, led plastic surgeons to assess for BIA-ALCL in patients presenting with a late seroma or mass. However, BIA-ALCL only contributes to a small proportion of these cases, which when combined with the absence of trauma, infection, or other explainable cause for late seroma underscores the need to expand the differential diagnosis to recognize other etiologies to explain what is otherwise referred to as “idiopathic.” In this narrative review, we present a broad overview of breast implant capsular pathologies associated with late presentation of intracapsular fluid accumulation or mass formation.

BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL)

BIA-ALCL is a T-cell lymphoma of the breast implant capsule that typically presents as sudden-onset unilateral breast swelling 7–10 years after implantation.[10, 11] While BIA-ALCL also occurs in native breast tissue, the incidence is greater in the presence of breast implants.[12] Further examination most commonly reveals a seroma or, less commonly, a mass.[13] Cordeiro *et al* and Nelson *et al* recently demonstrated that the incidence of BIA-ALCL in textured implant breast reconstruction patients may be as high as 1:355 to

559.[14, 15] Among patients with known implant type, all patients with BIA-ALCL were exposed to macrotextured implants, including 11% of patients who already had undergone exchange to a smooth device.[16] However, the pathophysiology linking macrotextured implants and BIA-ALCL remains unknown. Leading theories include genetic predisposition and chronic inflammation—potentially induced by implant-surface biofilm or shedding of silicone particles.[17] The U.S. Food and Drug Administration recently reported one case of BIA-ALCL in a patient exposed only to a smooth implant,[18] underscoring the inadequacy of our current understanding of the BIA-ALCL disease process.

The National Comprehensive Cancer Network (NCCN) has recommended guidelines for BIA-ALCL diagnosis and management.[19] First, suspected cases should undergo ultrasound or MRI with needle aspiration of any effusion or fine-needle aspiration of a capsular mass. The pathology is positive for BIA-ALCL if flow cytometry and immunohistochemistry demonstrate clonal CD30+ALK-T-cells. If the pathology is indeterminate, the specimens should be sent to a specialized center for further analysis. If the disease is confined to the capsule, the patient should have a complete capsulectomy. If there is an extracapsular mass, the patient should undergo complete capsulectomy with excision of the extracapsular mass but should also be referred to hematology for potential adjuvant chemotherapy or radiotherapy.

CAPSULAR PATHOLOGY PRESENTING WITH INTRACAPSULAR FLUID ACCUMULATION

Synovial Metaplasia

Synovial metaplasia often presents as a seroma or unilateral breast swelling and is usually found incidentally on pathology.[20, 21] Case reports have described synovial metaplasia as the etiology of an intracapsular fluid collection that was thought in one instance to be BIA-ALCL and in another to be a ruptured saline implant.[20, 22] Synovial metaplasia is a benign condition occurring in 40–77% of breast implant capsules independent of implant texture and fill.[23, 24] In response to microtrauma from the implant moving in the capsule pocket, the capsule attempts to repair itself by developing a synovial lining analogous to an articular joint.[21, 23–25] Synovial metaplasia is associated with time elapsed since implantation, with increasing prevalence during the first 5 years, and decreasing prevalence thereafter.[24, 26]

Clinically, entry of a pocket that has undergone synovial metaplasia will typically reveal a viscous, cellular fluid; diagnosis is confirmed through assessment of the capsule by pathology.[20, 21] Capsules that have undergone synovial metaplasia display a layer of cells with secretory properties on the inner lining.[21, 23, 25] While definitive diagnostic imaging modalities are lacking, synovial metaplasia occasionally shows capsular thickening in conjunction with peri-implant fluid.[22] This condition is managed by capsulectomy with or without implant exchange.

Capsular Epithelialization

Capsular epithelialization is a rarely reported, with only four reports published in the literature to date.[27–30] The reported presentations include non-specific unilateral breast

enlargement, breast implant extrusion, and contour irregularity with non-specific fluid on MRI.[27–30] The etiology of capsular epithelialization is unknown; leading hypotheses include ingrowth of epithelial cells from the wound margin, metaplasia of breast duct cells, or surgical seeding of keratinocytes at the time of breast implant placement.[27, 31]

Clinically, the few reports of capsular epithelialization describe scattered islands of epithelialization and cystic structures in the capsule, along with fluid whose consistency ranges from serosanguinous to milky and keratinaceous. Capsular assessment by pathology will typically reveal epithelial cells or keratinaceous debris, differentiating capsular epithelialization from other capsular pathology.[27–30] Capsulectomy to ensure removal of any residual intracapsular epithelial tissue appropriately treated this condition in case reports.

Late Hematoma

Late hematomas in breast implant patients usually present as unilateral swelling of the breast that is more commonly chronic and progressive but can on occasion present acutely.[29, 32–35] The exact incidence is unknown, and descriptions of late hematomas are limited to several case reports and small case series.[33, 36, 37] Many of the published cases have been deemed idiopathic, but some patients report an inciting traumatic event.[29, 32–35] Several causes have been attributed to their onset, including capsular tear, erosion of a capsular artery with prevention of retraction by the fibrotic capsule, chronic inflammation, and chronic microtrauma from motion of the implant in a contracted capsule.[29, 32, 33, 35, 36, 38, 39] After these inciting events, progression of late hematomas has been compared to that of chronic subdural hematomas, with small recurrent bleeds forming clots that create osmotic environments that slowly pull fluid into the capsule over time.[34]

To diagnose a late hematoma, computed tomography (CT), MRI, or ultrasound are used to identify fluid with or without an organized mass (clot). An aspirate of the fluid is sent for pathology and/or cytology for definitive diagnosis. The management of late hematoma involves evacuation of the hematoma, clot, and fluid from the breast pocket, capsulectomy, and coagulation of any bleeding blood vessels. Upon entering the pocket of a breast affected by late hematoma, the surgeon typically notices the presence of serosanguinous fluid, blood or a clot with varying degrees of organization, and possibly inflamed or granulation tissue.[29, 33, 37, 40] Pathology reports for the cases in the literature have described engorged blood vessels, which could represent the etiology of the sentinel bleed and reinforce the need for meticulous hemostasis.[29, 33]

Double Capsule

A double capsule is another cause of unilateral breast swelling. A double capsule is associated with a more chronic or indolent onset of unilateral breast effusion and more commonly occurs in patients with macrotextured implants.[10, 41, 42] The exact etiology of the double capsule is unclear but is thought to be either mechanical, infectious, or both. The mechanical hypothesis describes the integration of the textured implant into the capsule; then, as force is transmitted through the chest, the portion of the capsule adherent to the textured breast implant delaminates from the outer portion of the capsule. This results in the creation of a potential space and through micromotion of the two delaminated layers

of capsule, inflammation results and fluid accumulates.[41–43] The presence of biofilm at the implant-capsule interface has also been linked to delamination of the inner layer of capsule, which again results in the creation of a potential space for fluid to accumulate.[44]

A double capsule is usually diagnosed at the time of revision surgery. Although often an incidental finding, the presence of a double capsule may explain why the patient developed a recurrent seroma. The surgeon observes a capsule adherent to the implant and a residual capsule in the breast pocket. A double capsule is best managed with capsulectomy and implant exchange.

CAPSULAR PATHOLOGY PRESENTING WITH DEVELOPMENT OF A MASS

B-Cell Malignancy

B-cell lymphoma of the breast represents <0.5% of all breast malignancy.[45] Only eight case reports describing B-cell lymphoma in patients with breast implants have been published.[46–53] It is questionable whether implants play a causal role in B-cell lymphoma given that four of the nine reported patients also had systemic lymphoma, and only about half of these cases involved the luminal aspect of the implant capsule.[47, 50, 52–54] Of the different types of B-cell malignancy, large B-cell lymphoma is thought to be the most likely to be linked to implants because it can be activated by chronic inflammation in a manner similar to BIA-ALCL.[54]

In terms of clinical presentation, about half of the reported cases had breast pain and swelling, while others had axillary lymphadenopathy, recurrent fevers, and systemic symptoms.[47–53] Patients with any of these symptoms, especially in the context of a history of systemic lymphoma, should prompt consultation with a hematologist and surgical oncologist. Following the NCCN guidelines for BIA-ALCL workup will facilitate diagnosis and should include aspiration and cytology of any intracapsular fluid with CT or MRI as needed to better characterize a mass. A PET scan is also valuable for the evaluation of extra-mammary disease. Definitive management should be directed by a hematologist specializing in B-cell lymphoma, with the plastic surgeon and surgical oncologist offering surgical support for complete capsulectomy and excision of the mass if indicated.

Squamous Cell Carcinoma

Seven cases of squamous cell carcinoma in the breast implant capsule have been published,[28, 55–59] and our group recently treated another case. Squamous cell carcinoma arising from the capsule typically presents as unilateral breast pain and enlargement with possible axillary lymphadenopathy.[56, 58] Most of the reported cases have occurred in patients who have had their implants for more than 15 years and have incomplete knowledge or documentation of their history of breast surgeries (capsulectomies, exchanges, implant types and textures).[56, 58, 59] The etiology is thought to be similar to a Marjolin's ulcer, with chronic inflammation or irritation of a capsule that has undergone squamous metaplasia. Similar to capsular epithelialization, the source of the epithelial cells is debatable and could be seeding from surgical incisions, metaplasia of the breast ductal cells, or transformation of the capsular cells. Notably, free silicone injection into the breast has also been associated

with breast squamous cell carcinoma.[60] Squamous cell carcinoma of the breast also occurs in the absence of breast implants, albeit rarely, representing only 0.1% of all invasive breast cancers.[61]

Patients presenting with unilateral breast swelling, pain, and periprosthetic fluid collection or capsular mass should be managed using the NCCN BIA-ALCL guidelines to arrive at a diagnosis. The aspirated fluid is typically keratin-rich, and masses usually display dysplastic keratinized epithelium of capsule histologically.[55–59] While this is a rare disease, the devastating outcomes underscore the importance of rapid diagnosis and urgent management to maximize the survival of patients affected by breast implant capsular squamous cell carcinoma. Of the seven patients in the published case reports, four died from the disease. Once the tumor extends beyond the capsule, the risk of locoregional metastasis is high. Therefore, these patients should also undergo positron emission tomography (PET) to assess for spread of the disease and be promptly referred to surgical oncology. Surgical management should be deferred to the surgical oncologist but should at least include explant and capsulectomy. The reported cases have at minimum involved mastectomy and occasionally chest wall resection and lymphadenectomy. As with patients without implants who develop breast squamous cell carcinoma,[62] patients with capsular squamous cell carcinoma should also receive adjuvant chemotherapy and radiation therapy under the direction of a multidisciplinary tumor board. We recently treated a patient with capsular squamous cell carcinoma according to these management strategies, using neoadjuvant chemotherapy, mastectomy, and chest wall resection, resulting in disease-free survival over 2 years after reconstruction (Figures 1 and 2).

Breast Cancer

Only one case series describing breast cancer within the implant capsule has been published.[63] The authors of this paper and the case series acknowledge that this is probably due to underreporting. In the published series of three patients, patients either had multiple nodules along the implant capsule or a tumor invading the capsule. Interestingly, the tumor was found in the area of the capsule against breast parenchyma and was absent in the capsule against muscle in the case of subpectoral implants. All three patients presented with masses that had evolved, with satellite lesions and/or spread along the capsule.

Primary breast carcinoma occurs as frequently in patients with cosmetic implants as in patients without cosmetic implants.[64] The breast cancer pathology in this case series was not discussed; however, there was concern for tumor cells that invaded or spread to the outer vascular layer of the implant capsule from a mass that developed in the breast parenchyma. Given the vascularity of the breast implant capsule, it is hypothesized that this represents a vascular plane where the primary breast cancer could infiltrate and spread.

The management of a palpable mass in a patient with breast implants should follow the same guidelines as for a patient without breast implants. Providers should immediately schedule an ultrasound or MRI and promptly refer patients to a surgical oncologist. For breast implant patients, MRI may be preferred since it provides better resolution of the tumor and capsule than ultrasound. Ultimately, the surgical management of the tumor should be guided by the surgical oncologist, but if capsular involvement is suspected, a complete capsulectomy

should be performed due to the potential for hematologic spread of tumor cells through the vascular plane of the capsule.

Mesenchymal Tumors

Mesenchymal tumors represent 0.2–0.3% of all breast tumors, and 10% of mesenchymal tumors occur in patients with breast implants.[65, 66] Mesenchymal tumors arising from the breast implant capsule are even rarer, with only a few reported cases in the literature.[67–69] Mesenchymal tumors, in general, arise from the benign proliferation of fibroblasts and myofibroblasts and are associated with trauma, such as surgical trauma from implant placement.[70] In the breast, mesenchymal tumors can develop from smooth muscle cells in the breast ducts or chest wall muscles.[65, 71] Mesenchymal breast tumors are typically solitary and benign but locally invasive.[65] The association between breast implants and mesenchymal tumor development is debatable since the frequency of these tumors in patients with and without implants is similar.[66, 72]

As with any patient presenting with a breast mass, a thorough physical examination is important, including an assessment for lymphadenopathy, since mesenchymal breast tumors often present as a palpable mass that has grown over time. Detecting the tumor is easier on examination when it is superficial, but it can be easily missed if it is deep, such as on the deep surface of the pectoralis muscle. Additionally, these tumors usually are not accompanied by any lymphadenopathy.[65] In terms of diagnostic imaging, MRI is the best modality, followed by ultrasound; on the other hand, mammograms rarely detect mesenchymal tumors.[65, 73, 74] Ultimately, these patients should be referred to a surgical oncologist for further characterization of the mass, which is diagnosed by core biopsy showing spindle cells.[75, 76] Surgical oncologists manage the mesenchymal tumor by attempting a complete excision. Where it involves the breast implant capsule, a capsulectomy should be performed to reduce the risk of local recurrence.

MANAGEMENT RECOMMENDATIONS FOR A PERIPROSTHETIC EFFUSION OR MASS

The conditions described in this overview have been rarely described. However, plastic surgeons had a similar experience with BIA-ALCL, whereby the incidence was extremely rare. With increased recognition and screening, seromas and masses that were previously thought to be idiopathic have now been diagnosed as BIA-ALCL. We suggest that by following the NCCN guidelines for BIA-ALCL screening for more routine late seromas and masses, we might be able to assign a diagnostic reason for the approximately 90% of late seromas that presently arise from an unknown etiology.

Upon presentation of an implant patient with breast pain or swelling, providers should perform a physical examination, palpating for any fluid collections, masses, or lymphadenopathy. Providers should also assess for any concerning systemic symptoms. Then, providers should adhere to the NCCN BIA-ALCL screening guidelines for patients presenting with a late seroma or mass, which will diagnose many of these rare capsular pathologies. Ultrasound or MRI can be used to identify the presence of a fluid

collection or mass and should be followed by ultrasound-guided aspiration or biopsy and pathologic workup. For the most part, these pathologies, like BIA-ALCL, are also managed by capsulectomy, implant exchange, and consultation with other oncologists when extracapsular disease is present.

Plastic surgeons have given significant attention to the indications for different types of capsulectomy in light of concerns about BIA-ALCL and breast implant illness. The FDA does not recommend capsulectomy for asymptomatic patients concerned about disease. However, upon finding irregularities in the capsule, recent expert opinions suggest to surgically excise suspicious capsule.[77] Depending on the distribution of disease, this could result in a partial or total capsulectomy.[78] If there is extra-capsular involvement, the surgeon should consult surgical oncology and/or tumor board for additional guidance on excision. It is important, however, to appropriately counsel patients about the risks of capsulectomy and highlight that to date there is no data to describe the rate of complications.[78, 79]

Limited data exists regarding reconstruction or implant replacement after capsulectomy for capsular disease, in part due to the rare diagnosis. The best recommendations in this regard were published by *Lamaris et al* concerning reconstruction following treatment for BIA-ALCL.[80] They recommend immediate reconstruction if the disease is limited to the capsule, but to wait 6 to 12 months if an extra-capsular component exists. However, such management following BIA-ALCL is debated, and the most conservative approach is likely no immediate reconstruction even if the process is limited to the capsule.

Table I provides a summary of diagnoses and treatments for non-BIA-ALCL capsular conditions.

CONCLUSIONS

Breast implant capsules are dynamic tissues that change over time. However, as BIA-ALCL has taught us, the capsule can evolve to have significant clinical implications. In addition to BIA-ALCL, plastic surgeons should be familiar with the broad differential diagnosis for capsular pathology that could explain “idiopathic” late seromas or masses. Our knowledge about BIA-ALCL has grown tremendously since it was first described in 1997. Not only have we diagnosed and treated a rising number of BIA-ALCL cases over time, but we have also discovered that BIA-ALCL occurs far more frequently than ever imagined. Similarly, these rare capsular conditions may not be as rare as we think. By continuing to follow the NCCN BIA-ALCL guidelines for the management of late seromas and masses, we may soon understand with greater accuracy the true incidence, etiology, and clinical implications of these conditions arising from the breast implant capsule.

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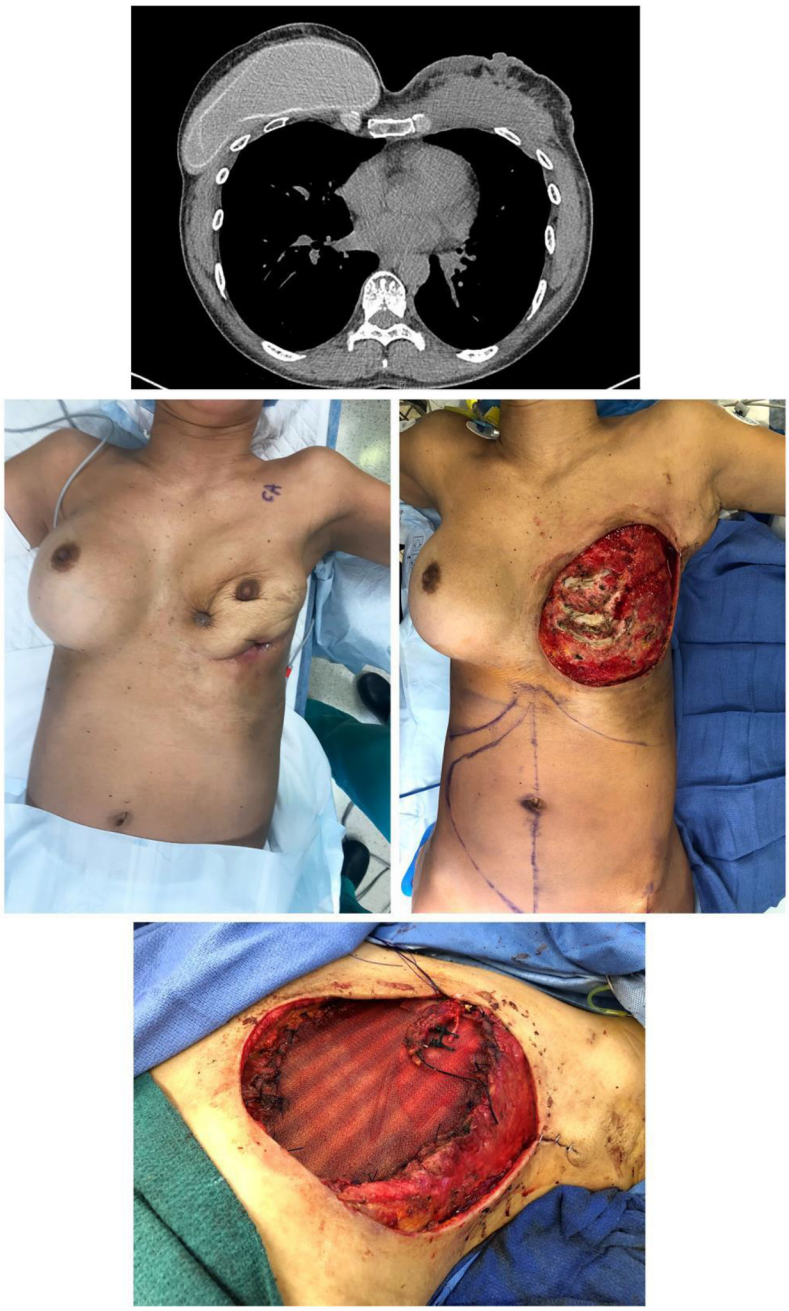

Figure 1.

Preoperative CT scan of the chest (A) and photo (B) of a forty-eight-year-old female patient with a history of bilateral breast augmentation show development of squamous cell carcinoma in the right breast implant capsule. Following diagnosis, the patient underwent chemotherapy followed by radical mastectomy and full thickness chest wall resection (C) and reconstruction with Phasix mesh (Bard Davol Inc., Warwick, RI) (D) and anterolateral thigh free tissue transfer.

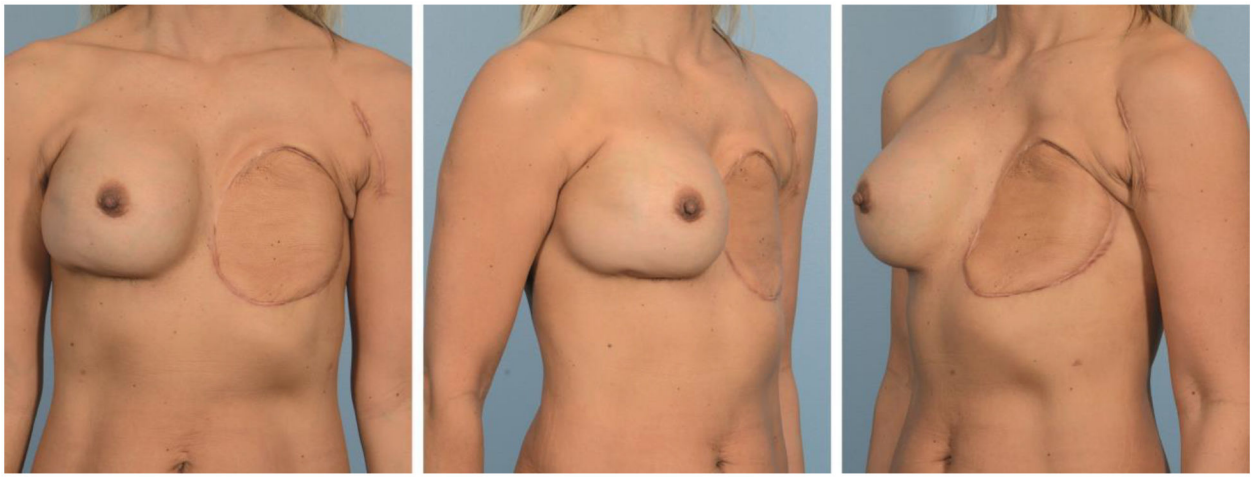

Figure 2.
Postoperative photos of patient at 3 years after reconstruction. She has remained disease-free.

Table I.

Non-ALCL Breast Implant Capsular Pathologies

Capsule Pathology	Incidence	Presentation	Diagnosis	Pathology	Management
Fluid accumulation					
Synovial metaplasia	40–77% of breast implant capsules[22, 23]	• Viscous fluid within capsule	• Pathologic assessment of capsule	• Viscous cellular fluid • Secretory synovial cells on inner capsule lining	• Capsulectomy with or without implant exchange
Capsular epithelialization	4 case reports/ series[26–29]	• Serosanguinous, milky, or keratinaceous capsule fluid	• Pathologic assessment of capsule	• Epithelial cells • Keratinaceous debris	• Capsulectomy
Late hematoma	Unknown	• Chronic, progressive swelling of the breast • Serosanguinous fluid, blood, or clot	• CT, MRI, or ultrasound • Pathology or cytology of fluid aspirate		• Evacuation of breast pocket, capsulectomy, coagulation of bleeding vessels
Double capsule	Unknown	• Chronic, indolent onset of unilateral breast swelling • Capsule adherent to implant with residual capsule in breast pocket	• Intraoperative assessment		• Capsulectomy with implant exchange
Mass					
B-cell malignancy	9 reported cases[46–53]	• Breast pain and swelling • B-symptoms (fever, night sweats, weight loss)	• Follow NCCN BIA-ALCL guidelines • Biopsy of mass	• Malignant B-cells	• PET scan • Referral to hematologist • Capsulectomy if indicated
Squamous cell carcinoma	7 reported cases[28, 55–59]	• Unilateral breast pain and enlargement • Possible axillary lymphadenopathy	• Follow NCCN BIA-ALCL guidelines • Biopsy of mass	• Keratin-rich fluid • Dysplastic keratinized epithelium	• PET scan for metastases • Referral to surgical oncologist and multidisciplinary tumor board

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Capsule Pathology	Incidence	Presentation	Diagnosis	Pathology	Management
					• Capsulectomy and explant • Chemoradiation
Breast cancer	3 reported cases[63]	• Palpable mass on physical examination	• Ultrasound or MRI • Biopsy of mass	• Breast cancer	• Referral to surgical oncologist • Capsulectomy if capsular involvement suspected
Mesenchymal tumor	Rare	• Palpable mass on physical examination	• MRI • Core biopsy	• Spindle cells	• Referral to surgical oncologist • Capsulectomy if capsular involvement suspected