Breast Implant–Associated Anaplastic Large Cell Lymphoma: What We Know

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) is a rare peripheral T-cell lymphoma, first reported in 1997. It is pathologically confirmed as a CD30-positive, anaplastic lymphoma kinase (*ALK*)–negative ALCL by immunohistochemistry. Unlike systemic *ALK*-negative ALCL, breast implant–associated disease has a much more favorable prognosis overall. In most cases, BIA-ALCL will present with delayed seroma more than 1 year after breast implantation indicated for either cosmetic or reconstructive purposes. The average onset of seroma presentation is 8 to 9 years after implantation. Breast implant–associated anaplastic large cell lymphoma may arise in one of two distinct forms: either in situ or infiltrative disease. In situ disease is confined within a seroma, while infiltrative disease may present with lymph node involvement either with or without palpable breast mass or tumor. Infiltrative disease has an overall worse prognosis in regards to disease-related mortality, up to 40% within 2 years. Appropriate pathological consultation with an experienced hematopathologist and oncologist is imperative when making a diagnosis of BIA-ALCL. There are several theorized risk factors associated with the disease; however, the exact pathophysiology is not yet known. Our objective in writing this review article is to provide an overview of what we know about the epidemiology, disease characteristics, and current management strategies. In doing so, we aim to bring awareness and familiarity to the advanced practitioner population in recognizing and treating BIA-ALCL.

Breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) is a rare peripheral T-cell lymphoma. As a result of incomplete reporting, coupled with the rareness of the disease, understanding its history has been challenging throughout the years. Despite its rarity, BIA-ALCL has gained much media attention in recent years, likely due to the fact that breast augmentation is the number-one cosmetic procedure performed in the United States each year (Doren et al., 2017).

The objective of this review article is to provide an overview of the most up-to-date information on the epidemiology, disease characteristics, and current management

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strategies for BIA-ALCL. Our hope is to bring awareness about BIA-ALCL to the advanced practitioner community and increase understanding of the most accurate diagnostic criteria for the disease, the appropriate evaluation and tests that should be ordered when BIA-ALCL is suspected, and the indications for operative management vs. systemic chemotherapy and/or radiation therapy. We will discuss the most updated information we have on BIA-ALCL, including initial presentation and diagnostic workup, disease characteristics, the National Comprehensive Cancer Network (NCCN) Guidelines for various treatment modalities, and considerations for future research.

DISEASE CHARACTERISTICS

There are a few different ways in which we know non-Hodgkin lymphomas can involve the breasts, including both B-cell and T-cell lymphomas. The vast majority of breast lymphomas are of B-cell origin, while lymphomas of T-cell origin account for less than 10% of cases. More specifically, there are three types of systemic ALCLs that have been known to involve the breast. These are anaplastic lymphoma kinase (*ALK*)–negative ALCL, *ALK*-positive ALCL, and cutaneous ALCL. When it is not associated with breast implants, *ALK*-negative ALCL is a systemic disease that rarely occurs within the breast tissue. It is usually diagnosed at a late stage and has an aggressive course (Aladily et al., 2012).

Breast implant–associated anaplastic large cell lymphoma, pathologically confirmed as a CD30-positive, *ALK*-negative ALCL, is unique in that the outcomes for patients' clinical courses are historically indolent and carry a good prognosis. In fact, most patients with BIA-ALCL can be treated with curative intent. According to a study referenced by Doren and colleagues (2017), it is estimated that the median overall survival rate is up to 93% at 3 years and 89% at 5 years. Patients in this study underwent a variety of treatments, including limited surgery, surgical excision, systemic chemotherapy, and radiation therapy. Most patients received two or more of these therapeutic interventions (Clemens et al., 2016).

There are two distinct pathologic forms of BIA-ALCL, the first and most common being in situ disease. This is defined as disease that is confined within the seroma. Often these in situ seroma presentations may be misinterpreted as benign seromas. The second form of BIA-ALCL is infiltrative disease, which involves palpable breast mass or tumor, or can include regional lymph node involvement without breast mass. Infiltrative disease may occur either with or without a periprosthetic effusion. Whether or not there is lymph node involvement, infiltrative disease is associated with significantly worse prognosis than in situ disease. Disease-related mortality for infiltrative disease has been found to be as high as 40% in 2 years (Kaarinten et al., 2017). It is not entirely clear whether the in situ disease progresses to infiltrative disease or whether these are two distinct entities that carry separate risks of dissemination (McCarthy & Horwitz, 2018).

According to an epidemiologic study by Doren and colleagues (2017), all documented cases of patients who developed BIA-ALCL had textured implants. There are only two cases that involved patients who had smooth implants. However, these two outliers had fragmented surgical histories and possible exposure to textured implants during multiple revisions. Given this data, it is widely accepted that there is a direct correlation between textured implants and the development of BIA-ALCL.

Any presentation of delayed seroma more than 1 year after implantation that cannot be explained by infection or trauma to the area should raise suspicions for BIA-ALCL (Clemens, Brody, Mahabir, & Miranda, 2018). Most patients will present with rapid onset of spontaneous fluid collection (60%–90%) or, less commonly, a capsular mass (10%–40%; Clemens et al., 2018). Effusion volumes can vary widely from 20 cc to 1,000 cc, and mean mass size is documented as 3.5 cm (Kaartinen et al., 2017). Less frequently, patients have presented with skin rash, pain, capsular contracture, and regional lymphadenopathy.

Cytologic analysis of BIA-ALCL will demonstrate findings of large, pleomorphic lymphoid cells with characteristic immunophenotype by flow cytometry and immunohistochemistry (IHC) staining (Table 1). Neoplastic cells are consistently CD30 positive and *ALK* negative. Over 80% of cases are positive for CD4 and CD43 IHC staining. 30% or more of cases are positive for CD3, CD45, and CD2 by IHC staining. Some cases may be posi-

Table 1. Cytologic Analysis of Breast Implant–Associated Anaplastic Large Cell Lymphoma

Morphology	Large, pleomorphic lymphoid cells, abundant cytoplasm, and horseshoe-shaped or "embryoid" nuclei with prominent nucleoli
Flow cytometry and immunohistochemistry staining	• CD30 positive and *ALK* negative • 80% positive for CD4 and CD43 IHC staining; 30% positive for CD3, CD45, and CD2 • Some cases are positive for CD15 and PAX-5

tive for CD15 and PAX-5, which may prompt the question of a differential diagnosis of classical Hodgkin disease, especially in the setting of infiltrative disease. On histopathology review, BIA-ALCL may be found in a variety of settings. The disease can be seen as individual anaplastic cells, cell clusters, or in coherent sheets lining the capsule surface or in the infiltrative stage (Kaartinen et al., 2017). If BIA-ALCL does spread beyond the implant capsule, it can be difficult to differentiate from systemic *ALK*-negative ALCL. Therefore, it is crucial that collaborative care be established between surgeons, medical oncologists, and radiologists in order for accurate diagnosis and staging to take place.

HISTORY AND EPIDEMIOLOGY

The first case of BIA-ALCL was reported in 1997 by Keech and Creech in their article "Anaplastic T-Cell Lymphoma in Proximity to a Saline-Filled Breast Implant" (Aladily et al., 2012). Breast implant–associated anaplastic large cell lymphoma began to gain national attention after the first safety communication was released by the US Food and Drug Administration (FDA) in 2011 (FDA, 2018). This announcement acknowledged the rarity of the disease and warned of a possible correlation to implants. However, that warning was placed under scrutiny due to a lack of appropriate epidemiologic data and relevance specifically to BIA-ALCL (Doren et al., 2017). Four years later, in 2016, the FDA updated their safety warning. It was also in 2016 that the World Health Organization (WHO) first provisionally classified BIA-ALCL as a separate subtype of non-Hodgkin T-cell lymphoma (Quintanilla-Martinez, 2017).

As of February 2018, 518 cases of BIA-ALCL have been reported across 25 different countries (Clemens et al., 2018). With the emergence of more cases over the past two decades, BIA-ALCL has gained international attention through efforts to better understand and treat the disease. In 2008, a Danish study reported a direct correlation between breast implants and incidence of ALCL, with an overall incidence of 0.1 to 0.3 per 100,000. This same study estimated the relative prevalence of BIA-ALCL in women with textured (vs. smooth) implants is 1 per 30,000 (Doren et al., 2017).

A more recent study published by de Boer and colleagues (2018) used a Dutch pathology database to determine the absolute risk of BIA-ALCL. Their findings suggested that risk was higher among different age cohorts. The absolute risk was identified to be 1 in 35,000 at 50 years of age, and 1 in 7,000 at 75 years of age. Calculations were made by using the number of BIA-ALCL cases with breast implants and total number of breast implants over five decades, per age category. However, it is yet to be determined whether age alone can be used as an independent risk factor or whether this data correlate to the overall length of exposure to the implant (de Boer et al., 2018; McCarthy & Horwitz, 2018).

It should be noted that there are more than 10 million women with implants around the world, and approximately 55,000 implants are placed in the United States every year for both cosmetic and reconstructive indications (FDA, 2018). Breast implant–associated anaplastic large cell lymphoma remains a rare disease entity and absolute risk factors are still not clearly understood. Continued data collection and collaborative care are essential to advance our current understanding of this rare disease.

DIAGNOSTIC WORKUP

If BIA-ALCL is suspected, initial workup should include evaluation by ultrasonography. In patients with BIA-ALCL, ultrasound has proven to have similar or better sensitivity and specificity when compared to computed tomography (CT)

and magnetic resonance imaging (MRI) in the evaluation of fluid collection, masses, and regional lymphadenopathy (Clemens & Horwitz, 2017). Magnetic resonance imaging or positron emission tomography (PET) should be used when ultrasound evaluation proves to be indeterminate for specific cases. In a study by Adrada and colleagues (2014), 44 patients with BIA-ALCL were evaluated, and mammography was found to be inferior to ultrasound in identifying the presence of an effusion vs. mass (sensitivity and specificity of 73% and 50% for mammography, respectively, vs. 84% and 75% for ultrasound, respectively). Therefore, mammography is not considered an acceptable imaging modality for patients with suspected BIA-ALCL (Clemens et al., 2018; Kaartinen et al., 2017).

Fine-needle aspiration of periprosthetic fluid collections should be performed, and histologic sample is recommended in findings of a solid mass. Immunohistochemistry is crucial in the inclusion/exclusion criteria for ALCL by CD30 staining. If the result is negative for CD30 or if there is an indeterminate diagnosis, patients can be referred to either a breast or plastic surgeon for clinical observation. Without evidence of a solid mass, tissue biopsy is not recommended as the first step in evaluation unless implant removal is performed. In this case, histopathologic evaluation of the capsule for possible ALCL infiltration is relevant for diagnosis and staging (Kaartinen et al., 2017). In the case of regional lymphadenopathy, excisional lymph node biopsy is indicated and recommended for further evaluation.

Breast implant–associated anaplastic large cell lymphoma is a rare disease entity that is unfamiliar to many institutions; therefore, an expert hematopathology consultation is essential. Suspicious pathology material should be sent for evaluation by a pathologist with experience. The pathologist should be told about a suspicion of BIA-ALCL prior to review, as certain cell markers may be pertinent to diagnosis that would not otherwise be ordered. It is also recommended that a secondary evaluation by a hematopathologist be requested if the original evaluation is inconclusive (Clemens & Horwitz, 2017).

Positron emission tomography is useful in evaluating associated capsular masses or chest wall involvement, or to demonstrate systemic spread to regional or distant lymph nodes. Active BIA-ALCL will be FDG-avid on a PET scan (Clemens & Horwitz, 2017). Baseline PET imaging is essential in establishing if disease is localized or disseminated.

Following confirmation of disease, patients should be scheduled for a consultation with a medical lymphoma oncologist as well as consideration of a surgical oncologist, both of whom should have experience with this disease. Recommended lab work includes a complete blood count with differential, comprehensive metabolic panel, and a lactate dehydrogenase level (Clemens & Horwitz, 2017). Bone marrow biopsy is often not indicated unless there is evidence, a high suspicion of systemic spread, or unless the patient's oncologist is looking to differentiate from other peripheral T-cell lymphomas. This decision can be left to the discretion of the patient's individual provider (Clemens & Horwitz, 2017).

STAGING OF DISEASE

The Lugano revision of the Ann Arbor staging system is commonly used to stage BIA-ALCL. Using this method, most cases of BIA-ALCL fall into stage IE (83%–84%), with disease limited to a single extranodal site (i.e., the breast or capsule involvement). Stage IIE is the second most common stage (10%–16%), with disease spread to local lymph nodes. Only 0% to 7% of cases fall into stage IV disease with this system (Clemens & Horwitz, 2017). However, more recently, The University of Texas MD Anderson Cancer Center has proposed a new staging system using the tumor, lymph node, and metastasis (TNM) classification, and it is now encouraged by the NCCN Guidelines (Clemens & Horwitz, 2017).

Under this newer classification, patients with stage I BIA-ALCL can have disease confined to the effusion, early capsule invasion, or mass aggregate that is confined to the capsule. Patients with stage I disease, including IA, IB or IC, do not have lymph node involvement or metastatic disease. Patients with stage II disease (either IIA or IIB) may also include patients with tumors that are locally invasive outside of the capsule, as well as those with involvement by one regional lymph node. Those with stage III disease all have locally invasive tumor outside of the capsule and regional lymph node involve-

ment. With this new system, most patients have stage IA disease (35%), but overall, patients are classified in a wide spectrum of stages compared to the Ann Arbor classification (Clemens & Horwitz, 2017; Table 2).

TREATMENT

Currently, there is no standard of care for the treatment of BIA-ALCL. With the collaboration of our nation's T-cell lymphoma experts, the NCCN Guidelines have recently been published and are available for public reference. Treatment can be given with intent to cure; strategies include monotherapy with surgical management, adjuvant systemic treatment, and initial systemic treatment. There are specific recommended post-treatment surveillance guidelines outlined in the NCCN Guidelines, and there are emerging treatment options for patients with relapsed disease. Decisions on the treatment of BIA-ALCL are variable and highly dependent on the patient's individual risk factors. The decision-making process should be shared between patient and provider, and each case should be individually based (McCarthy & Horwitz, 2018).

Table 2. Breast Implant–Associated Anaplastic Large Cell Lymphoma Tumor, Lymph Node, and Metastasis (TNM) Staging System

T: Tumor extent		
T1	Confined to effusion or a layer on the luminal side of capsule	
T2	Early capsule infiltration	
T3	Cell aggregate or sheets infiltrating the capsule	
T4	Lymphoma infiltrate beyond the capsule	
N: Lymph node		
N0	No lymph node involvement	
N1	One regional lymph node positive	
N2	Multiple regional lymph nodes positive	
M: Metastasis		
M0	No distant spread	
M1	Spread to other organs/distant sites	
Stages		
I	A	T1N0M0
	B	T2N0M0
	C	T3N0M0
II	A	T4N0M0
	B	T1–3N1M0
III	T4N1–2M0	
IV	TanyNanyM1	

Note. Adapted from Clemens et al. (2016); Clemens & Horwitz (2017).

For localized disease, treatment for BIA-ALCL is unlike that of other lymphomas in that most cases are curable with surgery. The optimal approach, with curative intent, for the management with patients with BIA-ALCL is surgical removal of disease by total capsulectomy and removal of the implant in addition to the capsule with negative margins. Consideration should be given to removing the contralateral implant as well. As most of these patients present with localized disease, surgery alone is sufficient. Complete mastectomy has not been shown to have a role in treatment, as the breast tissue is typically spared. In cases of infiltrative diseases, surgical removal should also include excision of any involved lymph nodes as well as any extracapsular masses, with negative margins (Kaartinen et al., 2017). Adjuvant therapy is not currently standardized, and an established approach to identify patients has yet to be developed. The decision to include adjuvant therapy in a patient's treatment plan should be a multidisciplinary decision with a team of experienced surgeons, oncologists, and radiation therapists. Adjuvant therapies include radiation and/or systemic chemotherapy. Patients presenting with disseminated disease are at higher risk for recurrence. If complete excision is not possible in this population, then neoadjuvant radiation therapy should be considered (Horwitz et al., 2018; Kim, Predmore, Mattke, van Busum, & Gidengil, 2015)

Advanced, widespread BIA-ALCL is rare and there is currently no standard of care for patients who fall in this category (Ferrufino-Schmidt et al., 2018). Patients with extensive disease have most often been treated with regimens similar to those for patients with systemic *ALK*-negative ALCL. Combination chemotherapy treatments include cyclophosphamide, doxorubicin (Adriamycin), vincristine (Oncovin), and prednisone (CHOP), CHOP with etoposide (CHOEP), or other anthracycline-based chemotherapy (Horwitz et al., 2018; Richardson et al., 2017).

If a patient had implants for reconstructive purposes following treatment for breast cancer, it is important to take into consideration their complete treatment history, as many breast cancer chemotherapy regimens are anthracycline based. If a patient has a history of significant anthracycline exposure, treatment modification is essential to avoid cardiotoxicity.

Management of refractory or recurrent disease is also not standardized and should be individualized. There have been reports that radiation or chemotherapy for local recurrence has been successful (de Boer et al., 2018; Loch-Wilkinson et al., 2017). Since patients with advanced presentation at initial diagnosis are treated as systemic ALCL, relapsed disease should be as well. Currently, brentuximab vedotin is an effective and FDA-approved treatment for relapsed ALCL and can be considered (Blombery et al., 2016; Di Napoli et al., 2018).

The NCCN Guidelines outline recommendations for post-treatment surveillance. Clinical visits, including a complete history and physical examination, are recommended every 3 to 6 months for the first 2 years following treatment, with CT or PET imaging at a maximum of every 6 months. After 2 years of active surveillance, follow-up is recommended as clinically indicated (Horwitz et al., 2018). There is no standard of care for reconstruction options. It is assumed that as textured implants have been associated with this disease, these should be avoided completely. These plans should be individualized based on a patient's complete disease history, treatment plan, current disease status, and preference.

DISCUSSION

As outlined, BIA-ALCL is an extremely rare subtype of non-Hodgkin T-cell lymphoma, and a thorough understanding of this disease is still being established. While recent media attention has garnered well-deserved attention for this rare disease, it should not distract from its rarity. A thorough workup and consultation with expert oncologists, hematopathologists, and plastic surgeons are essential for proper evaluation and diagnosis. What is still unknown includes clear risk factors and an understanding of underlying causes (theories, including a biofilm on the implant surface, genetic predisposition, repeated capsular trauma and capsular contracture, direct or indirect immunologic response, and direct toxic damage from silicone components, have all been hypothesized; Kaartinen et al., 2017).

It is important to note that in accordance with the FDA, all confirmed cases of BIA-ALCL should be reported to the BIA-ALCL Patient Registry and Outcomes For breast Implants and anaplastic large cell Lymphoma etiology and Epidemiology (PROFILE) registry (thepsf.org/profile). Accounting for confirmed cases through this national registry allows for additional data collection and aids further understanding and subsequent advances in this rare disease.

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

Breast implant–associated anaplastic large cell lymphoma is a rare subtype of non-Hodgkin T-cell lymphoma. Despite the rarity of this disease, it has gained significant mainstream media attention over the past few years. Therefore, this is an important topic for advanced practitioners to understand so that patient questions and concerns can be appropriately addressed.

It is known that a portion of patients undergoing reconstructive surgery do so after significant life-altering events, such as the development and treatment of breast cancer. Taking this into consideration, it can be suggested that a patient's decision to undergo reconstructive surgery can be linked to strong emotional ties. The mainstream media has addressed this topic through newspaper articles, television coverage, Facebook support groups, and more. It is not surprising that information found through these sources are emotionally charged. On a quick review, language used in these sources include the words "dying," "lawsuits," "devastating consequences," and "shame." Although not directly studied, one could theorize such information could lead to confusion and fear among patients who have undergone reconstructive surgery or are actively deciding to have breast augmentation surgery. Research dedicated to the psychological implications of this disease has yet to be published. Such studies have the potential to increase our understanding of the effects of this disease on a more holistic level by bringing a

greater awareness to not only the physical aspects of the disease but also the emotional implications.

As advanced practitioners, we play an integral part of a patient's care team model, and counseling patients on medical decision-making is an important part of our role on the team. Having a basic knowledge of this rare disease will facilitate more productive conversations with our patients while acting as a liaison to the current and accurate information and the most appropriate resources for their care.

CONCLUSION

Breast implant–associated anaplastic large cell lymphoma is a rare peripheral T-cell lymphoma. The first case was reported in 1997, and nearly 2 decades later it was finally classified by WHO as a separate subtype of non-Hodgkin lymphoma. This is a disease most often found in the localized state and carries an indolent course. We now have established treatment options, and overall, patients have a favorable prognosis. If suspected, proper workup and evaluation is essential for appropriate diagnosis. This includes expert, multidisciplinary consultation with an institution that is familiar with this disease.

It is important that the risk of developing BIA-ALCL, although small, be thoroughly discussed with women considering breast augmentation with implants for either cosmetic or reconstructive purposes. Although we are uncertain whether in situ disease and infiltrative disease are two separate entities, diagnosis in the localized early stage of BIA-ALCL is crucial, as outcomes for these patients are excellent (de Boer et al., 2018). By spreading awareness about BIA-ALCL, including the epidemiology and characteristics of the disease, we are hopeful that more advanced practitioners will feel comfortable in assessing these patients and gain familiarity with the appropriate diagnostic workup.

Disclosure

The authors have no conflicts of interest to disclose.

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