An Updated Approach and Understanding of Breast Implant–Associated Anaplastic Large Cell Lymphoma

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ABSTRACT

Breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) is a rare subtype of T-cell non-Hodgkin lymphoma that is usually localized to the fluid and capsule surrounding a breast implant. There have only been <1,000 cases and 36 deaths reported to date and the average patient presents 7 to 10 years following initial breast implant placement. Most patients present with delayed seromas, a breast mass, capsular abnormalities, lymphadenopathy, or cutaneous masses. Unlike other forms of non-Hodgkin lymphoma, most cases are cured with surgery alone. The challenge of BIA-ALCL surrounds its rarity—in regard to both its diagnosis as well as the limited available data to guide therapy for more advanced cases. Careful pathology evaluation to analyze both the fluid surrounding the capsule and the capsule itself is critical. Studies to identify which patients are at greater risk of development of this rare entity are ongoing.

Background and Epidemiology

Breast implant–associated anaplastic large cell lymphoma (BIA-ALCL) is an extremely rare subtype of T-cell non-Hodgkin lymphoma that most often behaves indolently, is usually localized to the breast implant region, and can be cured with surgery alone in the vast majority of cases. Moreover, it seems to be preventable by avoiding placement of textured breast implants—the apparent causative device.

BIA-ALCL was first described in 1997 and recognized as a provisional entity in the 2016 WHO classification of lymphoid neoplasms. To date, there have been 993 cases reported in the literature and 36 deaths related to the lymphoma. At least 620 of the reported cases have been associated with exposure to the Biocell macrotextured surface. Most often this disease presents with a delayed seroma, a fluid collection around the implant that arises more than 1 year after the placement of a textured implant device (either a tissue expander or a breast implant). Uncommonly, patients present with a breast mass, capsular abnormalities, lymphadenopathy, or cutaneous masses. The median time from placement of the implant to development of BIA-ALCL is 7 to 11 years, but cases have been seen as soon as 2.2 months after replacement of an implant and as long as 44 years from initial implant placement. Cases of BIA-ALCL have only occurred in women with a history of a textured implant. Although cases have occurred in individuals with smooth implants in place, these all had some previous exposure to textured devices or an implant of unknown type.

Although original estimates of the incidence of BIA-ALCL were 33 per 1 million people or 1 in 30,000 person years for those with a textured implant, other international series have shown that the risk ranges from 1:1000 to 1:10,000 implants. In the largest prospective series of a specific type of textured implant, which included 17,656 women receiving 31,985 salt-loss textured implants (Natrelle 410), 4 cases of BIA-ALCL cases occurred for an overall risk for Allergan Natrelle 410 implants of 1:2,207. A population-based study from the Netherlands showed that the risk of developing BIA-ALCL from a textured implant is 1:6,920. Another recent
series from Memorial Sloan Kettering Cancer Center suggests the risk could be as high as 1:450.14 However, in that series, patients operated on by a single surgeon, and who had reconstruction after mastectomy for breast cancer, were prospectively followed for a median of >8 years at a center where physicians, pathologists, and many patients are alert to the risk of BIA-ALCL. Therefore, that patient population could have had other unique risks and is currently an outlier in the literature. There have been some reports through the Danish National Registry that germline BRCA1/2 mutations may increase the risk of developing BIA-ALCL, with an estimated risk of 1:1,550.15 In other studies in patients with delayed seromas after textured breast implants, the risk of BIA-ALCL is estimated at approximately 10%,1,3-16,18 Therefore, although rare overall, the risk in variably defined “at risk” populations is by no means trivial, and the overall incidence of BIA-ALCL ranges between rare and uncommon. In our experience, many patients who underwent breast augmentation or reconstruction using textured implants chose them with the understanding that this procedure was associated with little known risk. The diagnosis and fear of the diagnosis have a significant psychological impact, and feelings of regret and anxiety can be especially intense, particularly as awareness of BIA-ALCL increases among patients and the general public.

Despite its overall rarity, BIA-ALCL has received significant public and media attention.19,20 By 2011, the FDA established a task force to further investigate the risk of cancer associated with textured breast implants. In December 2018, France’s National Agency for the Safety of Medicines and Health Products prohibited the sale and requested a voluntary recall of textured implants across 33 countries. In July 2019, the FDA requested a voluntary recall of Allergan textured breast implants, the most widely used textured implant that accounted for 91% of the known cases. Cases associated with textured implants from other manufacturing companies have been reported as well, and textured implants with a high surface area were reported to be associated with increased risk of BIA-ALCL.21 This led the FDA to provide a black box warning for all breast implants in 2020 and use of standardized informed consent.

Given that BIA-ALCL often presents more than a decade after implant placement and an estimated 10 million people worldwide currently have textured implants, patients will continue to present with possible BIA-ALCL for the foreseeable future, even as the suspension of new textured implants leads to a reduction and eventual elimination of BIA-ALCL over time.22 Patients with symptoms suggestive of BIA-ALCL (eg, late-onset seroma, breast swelling and/or erythema, changes around implant) need prompt and thorough evaluation. Given the low absolute risk of developing BIA-ALCL from textured implants and that patients usually present with symptoms even in early-stage disease, current guidelines from plastic surgery societies do not currently recommend uniform prophylactic removal of textured implants in the absence of signs or symptoms of BIA-ALCL.23 However, individual patients and their surgeons are increasingly opting for removal. Understanding who is at risk, recognizing the presenting features, and, when necessary, performing a thorough and expert pathology evaluation are essential to accurately diagnose BIA-ALCL or exclude the diagnosis as conclusively as possible.

**Workup and Management**

The pathologic workup of cases of suspected or confirmed BIA-ALCL was recently consolidated into a comprehensive guideline.24 Because most patients present with a seroma surrounding the implant, ultrasound-guided fine-needle aspiration is the most common procedure used to establish the diagnosis. Periprosthetic benign fluid collections are common, and therefore a larger volume of fluid collection (10–50 mL) is recommended to better assess for the entity via cytopathology smears, cell block with immunohistochemistry, flow cytometry and, when possible, molecular genetic studies.

BIA-ALCL is characterized by the expression of larger aberrant lymphocytes that express CD30 and often CD4, but often lack expression of CD3 or CD5 (Figure 1A, B).24 Because these are often surface CD3–negative, gating for CD3 to evaluate for a T-cell population can lead to false-negative evaluation.23 Reactive processes and other even more rare lymphomas may also express CD30 and should be excluded. Molecular testing for T-cell receptor gene rearrangements can be helpful because results are often positive in BIA-ALCL.5,26

It is advisable that all cases undergo implant removal and complete capsulectomy, which should be bilateral if textured implants are present in both breasts. Complete evaluation of the entire breast capsule for tumors or focal areas to assess for more advanced BIA-ALCL is important and involves examination of multiple sections.24 We also endorse inking or marking the surgical specimen to allow orientation back to the patient to identify areas at risk if any mass or capsular penetration are identified.24 Understanding the location of tumor within the capsule can be helpful in planning further therapy if more advanced disease is identified.

For histologically confirmed cases of BIA-ALCL, a multidisciplinary approach between medical oncology, surgical oncology/plastic surgery, and hematopathology is important. Given the increasing understanding of the disease and emerging standard approaches, NCCN has outlined guidelines for the management of patients with BIA-ALCL (Figure 2).27,28 Additionally, new cases should be reported to the MedWatch website and PROFILE
(Patient Registry and Outcomes For breast Implants and anaplastic large cell Lymphoma etiology and Epidemiology) registry, which is a prospective registry of BIA-ALCL cases developed by Plastic Surgery Foundation, American Society of Plastic Surgeons, and the FDA, which is a prospective registry and repository for data on BIA-ALCL.

Unlike other forms of lymphoma, staging of this disease is primarily surgical and uses a TNM staging criteria (Figure 3). We recommend presurgical PET/CT for patients with suspected or confirmed BIA-ALCL who are undergoing implant removal and capsulectomy in order to optimally stage the chest, axilla, and body. Staging by imaging after surgery may be confounded by postoperative changes, making it difficult to appreciate residual lymphoma. Moreover, lymph node involvement in BIA-ALCL can be subtle and has been seen not only in axillary lymph nodes but also in intramammary lymph nodes, which are not assessed by surgical resection. In other T-cell lymphomas, PET/CTs have been able to identify disease that would not have been recognized on a CT with contrast in up to 30% of cases, and our experience suggests PET/CT as an optimal way to identify suspicious nodes as well as rule out more disseminated disease prior to surgery. If suspicious locoregional lymph nodes are seen during initial staging, we suggest biopsy of these lymph nodes during surgical staging or even preoperatively through radiologic guidance, because repeat biopsies in that region during the postoperative period can be technically challenging.

More than 85% of patients diagnosed with BIA-ALCL will have stage I disease or disease limited to the seroma or the seroma and the capsule (Table 1). In these patients, surgical management with a complete en block surgical resection of the capsule and implant is associated with a 95% disease-free survival at 5 years without additional therapy. In contrast, those who did not have a complete resection had an 11% chance of being disease-free at 5 years. This underscores the importance of an optimal surgery. Because contralateral BIA-ALCL at the time of diagnosis has occasionally been seen, we advise bilateral implant removal and capsulectomy in patients with confirmed BIA-ALCL when possible.

For patients who present with advanced-stage disease (stage ≥II), the optimal treatment remains unclear. Although this only affects approximately 15% of patients with this disease, the event-free survival for those with stage II and III disease at 5 years is 63% and 71%, respectively. Furthermore, deaths from lymphoma have been reported in up to 20% of patients with advanced-stage disease. A total of 36 deaths have been reported from BIA-ALCL to date, predominantly among those who presented with more extensive disease. Given the rarity of BIA-ALCL, there are no true prospective experiences to define optimal therapy.

Figure 1. (A) PET/CT image of a patient presenting with left-sided breast implant-associated anaplastic large cell lymphoma. (B) Histologic examination of the capsule demonstrates focal involvement of large atypical lymphocytes in the fat beyond the capsule. (C) Immunohistochemistry shows that these cells stain positive for CD30.
For patients with disease limited to the breast or chest wall, with tumors or incomplete resection, we often recommend radiation therapy while acknowledging that there are few data to suggest an optimal treatment approach. However, the decision to use radiation should be individualized based on prior radiation, planned fields, size of residual mass, and other patient-specific factors. Similarly, brentuximab vedotin has been reported in the adjuvant setting.³³,³⁴ In patients with advanced BIA-ALCL and prior breast radiation and/or anthracycline-based chemotherapy, which is often the case in women with a history of breast cancer, we recommend an individualized, multidisciplinary approach based on their particular risks and pattern of lymphoma, because these cases can be particularly challenging.

For patients with lymph node involvement or disease outside the breast and lymph nodes, we recommend use of brentuximab vedotin with cyclophosphamide/doxorubicin/prednisone (BV-CHP).³⁵ The combination of BV-CHP was compared with cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) in an international randomized, double-blind study that showed an improvement in progression-free survival.
survival and overall survival in CD30+ peripheral T-cell lymphomas. Although no patients with BIA-ALCL were treated on this study, we extrapolate this approach from the high complete response rate and significant overall survival benefit in systemic ALCL. Single-agent use of BV has also been reported both in the adjuvant and neoadjuvant setting but not widely studied.34,36,37

Genomic Landscape of BIA-ALCL

Recent series have started to elucidate the genomic landscape of BIA-ALCL. Unlike systemic ALCL, rearrangements of ALK, DUSP22, and TP63 have not been seen in BIA-ALCL. Similar to other forms of ALCL where the JAK/STAT pathway is frequently activated, mutations in this pathway (JAK1, STAT3, SOCS1) have been recurrently seen in BIA-ALCL.38–40 Mutations in epigenetic regulators, such as TET2, TET3, ARID4B, KDM5C, KDM6A, KMT2C/D, SMARCB1, SETD2, DNMT3A and CREBBP, have also been seen in up to 74% of cases.39 Both somatic and germline mutations in TP53 have been reported in BIA-ALCL.38–41 Additionally, one series suggested that the risk of BIA-ALCL might be associated with a history of germline BRCA1/2 mutations, as mentioned earlier.15

Conclusions

BIA-ALCL remains a rare complication that occurs in individuals who have had textured breast implants. Although obtaining a diagnosis can be challenging, it is not particularly complex. The challenge arises more from its rarity. In many centers, aspirations of seromas around implants are performed by radiologists or surgeons with experience and expertise in breast cancer, and are not reviewed by hematopathology. In other

Table 1. MD Anderson TNM Staging for BIA-ALCL

<table>
<thead>
<tr>
<th>TNM or Stage Designation</th>
<th>Description</th>
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<tbody>
<tr>
<td>T: tumor extent</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Confined to effusion or a layer on luminal side of capsule</td>
</tr>
<tr>
<td>T2</td>
<td>Early capsule infiltration</td>
</tr>
<tr>
<td>T3</td>
<td>Cell aggregates or sheets infiltrating the capsule</td>
</tr>
<tr>
<td>T4</td>
<td>Lymphoma infiltrates beyond the capsule</td>
</tr>
<tr>
<td>N: lymph node</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No lymph node involvement</td>
</tr>
<tr>
<td>N1</td>
<td>One regional lymph node</td>
</tr>
<tr>
<td>N2</td>
<td>Multiple regional lymph nodes</td>
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<tr>
<td>M: metastases</td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No distant spread</td>
</tr>
<tr>
<td>M1</td>
<td>Spread to other organs or distant sites</td>
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Stage

<table>
<thead>
<tr>
<th>Stage</th>
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<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
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<tr>
<td>IB</td>
<td>T2N0M0</td>
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<tr>
<td>IC</td>
<td>T3N0M0</td>
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<tr>
<td>II A</td>
<td>T4N0M0</td>
</tr>
<tr>
<td>II B</td>
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<tr>
<td>III</td>
<td>T4N1–2M0</td>
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<tr>
<td>IV</td>
<td>TanyNanyM1</td>
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Abbreviations: BIA-ALCL, breast implant–associated anaplastic large cell lymphoma.

Clinical and pathologic staging of BIA-ALCL follows the MD Anderson Solid Tumor Staging System modeled after the AJCC TNM stages. Using this system, patients with BIA-ALCL have a spectrum of disease from stage IA (35.6%, effusion only), IB (11.5%), IC (13.8%), IIA (25.3%), IIB (4.6%), III (9.2%), to IV (0%). Adapted from Mehta-Shah N, Clemens MW, Horwitz SM. How I treat breast implant–associated anaplastic large cell lymphoma. Blood 2018;132:1891, with permission.

Figure 3. Schematic demonstrating that BIA-ALCL typically presents in the seroma surrounding the breast implant. The lymphoma is usually contained within the fibrous capsule and distinct from breast parenchyma. BIA-ALCL typically is isolated to within the fluid and/or inner wall of the capsule, although invasion into or beyond the capsule is less commonly seen and associated with a worse prognosis. Abbreviation: BIA-ALCL, breast implant–associated anaplastic large cell lymphoma. From Mehta-Shah N, Clemens MW, Horwitz SM. How I treat breast implant–associated anaplastic large cell lymphoma. Blood 2018;132:1891, with permission.

KMT2CD, SMARCB1, SETD2, DNMT3A and CREBBP, have also been seen in up to 74% of cases.39 Both somatic and germline mutations in TP53 have been reported in BIA-ALCL.38–41 Additionally, one series suggested that the risk of BIA-ALCL might be associated with a history of germline BRCA1/2 mutations, as mentioned earlier.15
cases, seromas may be therapeutically aspirated without pathology evaluation. Therefore, specific and adequate evaluation for BIA-ALCL may not be regularly performed. Samples may not be sufficient in volume or appropriately processed to maximize the workup of a relatively small number of diagnostic cells. An initial review aimed at ruling out breast cancer can leave the specimen inadequately evaluated and/or inadequately processed to rule in or out BIA-ALCL, potentially leading to a missed or a delayed diagnosis as well as findings of atypical or reactive lymphocytes but insufficient information to confirm a benign seroma. False-negatives during a repeated attempt to make a diagnosis can occur when seromas rapidly accumulate following initial aspiration due to a dilutional effect. And lastly, for those with diagnostic or suspicious aspirations or biopsies, adequate presurgical evaluation allows optimal oncologic decision-making for the minority of patients who are not cured by implant removal and capsulectomy alone. Awareness and suspicion of BIA-ALCL is a prerequisite to making an accurate diagnosis, and for many individuals, a multidisciplinary approach is optimal for diagnosis and management.

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References