Commentary

Commentary on: Lymphomas Associated With Breast Implants: A Review of the Literature

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> "If language is not correct, then what is said is not what is meant; if what is said is not what is meant, then what must be done remains undone; … if justice goes astray, then people will stand about in helpless confusion. Hence there must be no arbitrariness in what is said. This matters above everything."[1]
> Confucius (551–479 BC)

Epidemiological studies and previous meta-analyses have shown that breast implant–associated anaplastic large cell lymphoma (BI-ALCL) is a distinct type of T-cell lymphoma involving the capsule or effusion surrounding a breast implant. A United States Food and Drug Administration safety communication in 2011 prompted the American Society of Plastic Surgeons (ASPS) to initiate a patient registry, include BI-ALCL language in patient consent forms warning of this potential malignancy, as well as pressured implant manufacturers to include the same in package inserts. Despite being first described 18 years ago, little progress has been made to understand the etiology or molecular pathogenesis of this lymphoma. In addition, BI-ALCL remains unfamiliar or misunderstood by many oncologists, surgeons, radiologists, pathologists, and patients.

In many ways, the authors present a timely and much needed literature review on previous case reports of lymphoma and breast implants.[2] The manuscript supports several pertinent findings, including that the presentation of ALCL is a spectrum with occasional disease-related death, that the presence of mass portends a worse prognosis, that cases are not isolated to a particular type of implant, and that improved global awareness is needed. The authors are to be commended for trying to make further sense of a very rare disease that has been sporadically reported over the last two decades. More disease-focused manuscripts are needed on BI-ALCL as diagnosis and treatment of these patients is commonly delayed months and, in some cases, years. However, with so little known on this disease, it is absolutely critical that more recent reports should accurately report details of the circumstances of the disease, the pathologic findings, and detailed therapeutic approaches, to avoid misdiagnosis and misinformation. Therefore, a meta-analysis needs to be as accurate as possible, be a synthesis of previous findings, and offer physicians guidance for moving forward.

Accuracy in patient details is critical and requires constant revision and dogged persistence. There is a consistent phenotype reported in most cases of BI-ALCL, with strong expression of CD30 and almost all cases reported as anaplastic lymphoma kinase negative. The criteria used to identify cases at our institution are listed in Table 1 and have been previously reported.[3,4] The accurate diagnosis of BI-ALCL requires that the lymphoma cells are found within an effusion or lining the capsule that surrounds an implant. Some of the reported lymphomas were not found attached with the implant or capsule, and their inclusion is misleading, since these cases may represent a different disease that happens to occur in patients with implants. For instance, in Kraemer et al[5] the patient had device explantation nearly a decade before symptoms of a systemic B cell lymphoma developed. The lymphoma was never found in the breast or the axilla, just in the bone marrow. When determining if a patient has BI-ALCL, it must be differentiated from either systemic ALCL, primary cutaneous ALCL, or from primary breast lymphoma (PBL). BI-ALCL is distinct from PBL, which is a disease of the breast parenchyma, representing 0.04-0.5% of breast cancers and 1-2% of all lymphomas.[6]

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Table 1. Criteria for Diagnosis of Breast Implant–Associated Anaplastic Large Cell Lymphoma

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

PBL is predominantly a B-cell lymphoma (65-90%)[7,8] while BI-ALCL is a T-cell lymphoma.[9,10] PLB is radiographically distinct from BI-ALCL, as has been previously reported.[6,11] The authors' choice to focus on the concept of multiple different types of "lymphomas" related to breast implants is inaccurate and the authors do not provide evidence for this assertion. The authors do not discuss the most likely possibility of the coincidental association of systemic lymphomas in patients with breast implants. Furthermore, the authors do not provide evidence on the anatomical relationship of the lymphoma with the implant or capsule: these are critical pieces of information to render an accurate diagnosis of BI-ALCL. Device causality or even a loose association with other types of lymphomas is not supported. The threshold for "an association" cannot be a single case study, and at this time, these case reports remain outliers in relationship to BI-ALCL. There is a hazard in lumping together primary cutaneous ALCL, B cell lymphomas, or systemic lymphomas, which have a different pattern of disease progression, treatment, or prognosis. Patients with early stage BI-ALCL require surgery but may not require chemotherapy. In contrast, it is not accepted that other lymphomas are treated primarily with surgery, and depending on disease manifestation and staging, they may require adjunctive treatments.[12] The current uncertainties on diagnosing BI-ALCL are reflected in the wide spectrum of therapeutic approaches with various outcomes, and most patients with BI-ALCL receiving chemotherapy (69%), radiation therapy (55%), and autologous stem cell transplant (14%).[13]

Past literature reviews have been helpful in synthesizing the few known cases to propose etiologic mechanisms and successful patterns of treatment and have also led to the realization over the last several years of a near annual doubling of reported cases, which is also our experience with newly diagnosed patients. As we proceed forward in understanding this disease, aggregated data must include updated patient information, therapeutic interventions, and disease outcomes beyond what the original case report stated. This requires contacting original authors for extended follow-ups to determine treatment strategies, current disease states, and, most importantly, inquire whether the original report is still valid. Some authors have noted on reevaluation of pathology that the original report was mistaken in some way, which should be taken into account by cross-checking with corresponding authors.

Based on our experience with diagnosis and management of 21 patients with BI-ALCL at MD Anderson Cancer Center, we are generally in agreement with many of the technical aspects of BI-ALCL treatment discussed by the authors. Specifically, the authors note mandatory cytologic evaluation on a delayed peri-prosthetic fluid collection with a need for histopathologic evaluation of the capsule. Although the authors mention that textured implants may lead to effusion, a delayed effusion beyond 1 year of implantation should raise the suspicion of BI-ALCL. The authors insist that infection is one of the most common causes of effusion around implants, but there is no support for this assertion in the literature, except for their repeated statement. Similarly, in our experience, none of more than 20 patients of BI-ALCL who had the effusion cultured had bacterial growth. For correct nomenclature, we consider that the denomination of seroma is a misnomer, since seroma indicates a serous effusion, a relatively acellular, protein-poor fluid collection, while BI-ALCL patients demonstrate malignant effusion, which is viscous due to the high protein content and the presence of malignant cells. CD30 immunohistochemistry highlights lymphoma cells, and is particularly useful when lymphoma cells are scant. Similarly, the evaluation of any suspicious lesion in the capsule requires CD30 immunohistochemistry. Until we better understand the distribution of disease on capsules, generous sampling of capsules in cases suspected of BI-ALCL should be performed. Clinical evaluation should include palpation and imaging of regional lymph nodes. For management of the disease, our institutional approach is to perform resection of the disease with a surgical oncologist in combination with a plastic surgeon, and we feel this dual approach is essential. Surgical treatment includes primarily implant removal and total capsulectomy, with complete excision of any associated mass and negative margins on final pathologic evaluation. Excisional biopsy of any suspicious lymph node is recommended; fine needle aspiration or needle biopsies of lymph nodes should be discouraged because of the false negative results that are a consequence of the focal nature of the disease. Determination of optimal treatment will require prospective multicenter series, which are ongoing. The evidence of the literature and our own experience shows that BI-ALCL is a distinct entity and clearly different from primary cutaneous ALCL, for which the term CD30+ lymphoproliferative is occasionally used, depending on the clinical behavior of the disease, which can be waxing and waning. On the contrary, there is no evidence of spontaneous regression of disease once BI-ALCL is established, thus the suggestion of the authors that this disease should be labeled as a lymphoproliferative disorder and not a lymphoma is misleading.[13]

Guidance for the future of BI-ALCL research is well articulated within the manuscript. Obtaining mutational analyses and understanding the process of abnormal genetic transformation will lead to the recognition of modifiable risk factors and the identification of susceptible populations. Until that time, physicians who encounter these cases must report confirmed BI-ALCL patients. The ASPS and the Plastic Surgery Foundation established the Patient Registry and Outcomes For Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology[14] registry as a mechanism to track these patients over time. Many surgeons have been hesitant to report cases, and barriers to reporting must be addressed by our national societies so that we can expediently determine precise demographics and optimal treatment algorithms. Or, as the above quote was paraphrased by Wyatt Earp, "Fast is fine, but accuracy is everything".[15]

Disclosures

Dr Clemens has consulted for Allergan, Inc. (Irvine, CA). Dr Miranda has nothing to disclose. Both physicians were their respective National Societies' representative to the 2014 RAND Corp. Panel Consensus on BI-ALCL in Washington, DC.

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