

BIA-ALCL: weathering the challenges of a rapidly changing climate

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Through the collaboration of an oncologist and a plastic surgeon, breast implant associated anaplastic large cell lymphoma (BIA-ALCL) was first described in a 1997 case report.

⁽¹⁾ On July 24th 2019, the US Food and Drug Administration (FDA) called for a Class I recall of Allergan Biocell® texture breast implants and tissue expanders, ultimately resulting in a worldwide recall.⁽²⁾ The FDA classifies recalls by a numerical designation (I, II, or III) indicating the relative degree of health hazard, with class I the most serious and signifying “a reasonable probability that the use of, or exposure to, the violative product will cause serious adverse health consequences or death.” For many plastic surgeons, this announcement came as a surprise, however this decision was expected, evidence-based, and a result of 22 years of data on an iatrogenic malignancy. This editorial will describe the rapidly changing regulatory environment regarding breast implants and BIA-ALCL as well as address frequent misconceptions of the disease.

BIA-ALCL is a lymphoma based on pathology and clinical course, and therefore this malignancy is neither benign nor a lymphoproliferative disorder according to the World Health Organization.⁽³⁾ Delayed seroma (greater than 1 year from implantation) is by far the most common presentation for BIA-ALCL in roughly 70% of cases.⁽⁴⁾ Twenty percent of cases present with a breast mass, adjacent to the implant capsule and the remainder, less than 5%, present with regional lymphadenopathy, distant metastasis, an aggressive capsular contracture, breast pain and/or a breast rash.⁽⁴⁾ Very few cases of BIA-ALCL have been asymptomatic and only found incidentally at time of mastectomy, implant exchange, or other unrelated procedure. BIA-ALCL is exclusively associated with a history of a textured surface device, and there are no patients, case reports or case series to date with a clinical history of only smooth surface devices. Smooth surface implants dominate the US and Canadian markets, whereas textured surface implants in general are preferred by surgeons outside of these two countries.

Traditionally, BIA-ALCL has been referred to as rare, extremely rare, and akin to being “struck by an asteroid.” Our updated understanding of risk of disease now ranges from

1:440 to 1:86.000 depending on implant-specific risk.^(5,6) Therefore, *emerging* may be a more apt descriptor of prevalence until a more certain risk estimate is reached. The FDA now reports that when manufacturer was known, 91% of 573 reported world cases involved an Allergan Biocell device, and noted Allergan was disproportionately over represented when compared to other manufacturers.⁽²⁾ These findings directly informed and lead to the FDA’s recent recall decision. The FDA’s recall came after earlier regulatory decisions to restrict the sale of Allergan Biocell in 38 countries across Europe, Africa, Asia, and South America. Importantly, the FDA does not recommend prophylactic explantation/capsulectomy in existing patients with a Biocell implant. Heavy media attention has led to generalized concern by patients about all implants and in particular textured surfaces. A healthy patient may request explantation and capsulectomy, however there is no data that an implant exchange, partial capsulectomy, or total capsulectomy modifies the future risk of development of BIA-ALCL in a patient who is disease free with a textured implant history. Therefore, like the FDA, we discourage prophylactic interventions. Patients have developed BIA-ALCL with a history of a retained scar capsule, a history of only simple implant exchange, and some patients have been told they received a total capsulectomy and still ultimately developed disease which calls into question whether “risk reduction” is possible or necessary. The vast majority of patients will remain disease free. The complication risk of a surgical capsulectomy and implant exchange is significantly greater than the incidence of developing BIA-ALCL. Reconstruction patients should also be advised that their breast shape may change following a complete capsulectomy and that this procedure may devascularize overlying skin and flaps. Thoroughly discuss all benefits and risks with your patient to help her make an informed decision about implants that is best for her and her health.

For patients with confirmed or suspected BIA-ALCL, current National Comprehensive Cancer Network (NCCN) guidelines advise on obtaining a reliable diagnosis and an evidence based approach to treatment.⁽⁷⁾ Patients with BIA-ALCL typically present with a rapid-onset large volume delayed seroma around a textured implant. “Trace fluid” seen around

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a breast implant is a common finding, likely benign, and does not require screening or further testing. If the amount of fluid is symptomatic and allows for aspiration, then this fluid can be sent for CD30 immunohistochemistry, especially if found around a textured implant. Note that volumes of aspirate less than 50 ml may be unreliable for detecting disease as are samples taken after previous serial aspirations. CD30 positivity coupled with large anaplastic cells on cytology, ALK-, and a single T-cell clone on flow cytometry is pathognomonic for BIA-ALCL. CD30 is a relatively inexpensive and common pathology stain, however surgeons may find difficulty obtaining this test in some rural areas. Unfortunately, routine pathology or cytology alone will frequently miss the diagnosis. CD30 immunohistochemistry is essential as a screen for the disease, and surgeons without local access to this laboratory test should send specimens to their nearest tertiary center for evaluation. Please note, there is a small (1-5% of circulating lymphocytes) incidence of CD30 cells in 'normal' seroma specimens. Therefore, "low" or "scant" CD30 positivity of normal shaped lymphocytes by itself is not reflective of disease and may be benign inflammation.

For confirmed cases of BIA-ALCL, *En bloc* resection of implant and capsule with negative margins, is the preferred treatment for the majority of patients.⁽⁸⁾ BIA-ALCL in its earliest stage is confined to the fluid around an implant and therefore scar capsules may be pathologically free of disease in a patient with a confirmed diagnosis. In general, BIA-ALCL is indolent and slow growing, but mass lesions, grossly invasive disease, organ metastasis, and death occur in a relatively small subset of patients. In most such advanced cases, the time from initial diagnosis to definitive surgery was prolonged many months without treatment. A total capsulectomy without appreciating extent of disease in a BIA-ALCL patient may leave residual disease which has been reported to lead to hyperprogression with adverse sequelae such as organ and bone marrow metastasis. Thus, early intervention for diagnosis is advised in patients presenting with an effusion more than one year after cosmetic or reconstructive implantation. The optimal management of patients with advanced disease is not established, but most have been approached with both surgical excision and targeted immune therapy directed against CD30. For the majority of patients with a timely diagnosis and proper treatment, the prognosis is excellent.

While BIA-ALCL has been reported for over 20 years, many countries around the world are only recently reporting their very first cases just in the past year. It has become clear that BIA-ALCL cases will not be found unless actively searched and found. Disease awareness and centralized reporting to registries is essential. Within the US, the American Society of Plastic Surgeons established the PROFILE (www.theprsf.org/PROFILE) registry in 2012, and collects granular data on demographics, treatment strategies and outcomes of

patients. Great strides have been made in the understanding of this disease within a relatively short time period, however these accomplishments were only possible through the collaborative efforts of surgeons who encountered cases. Within the FILACP community, surgeons are encouraged to reach out to their local national societies to report cases, and actively participate in finding solutions for all of us.

We still have an incomplete understanding of disease genesis and its natural history, particularly related to precursor lesions, which have not been fully defined. The advanced end of the disease spectrum requires better definition, as such cases result in high morbidity and mortality. The overall mortality rate for BIA-ALCL is approximately 5%.² Unanswered questions relate to rapid low-cost screening alternatives, inciting factors, genetic abnormalities, and optimal systemic therapy. The relationship of BIA-ALCL to other forms of ALK-negative ALCL is not fully resolved, and rare cases have been reported with other types of surgical devices such as gluteal implants. What is clear is that BIA-ALCL is a lymphoma based on pathology and clinical course, and NCCN guidelines are the standard for the diagnosis and management of BIA-ALCL. With increased international regulatory scrutiny, plastic surgeons must stay abreast of a rapidly changing climate to meet the needs of their patients.

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