Anaplastic Large Cell Lymphoma Associated with Breast Implant (LACG-AIM): A Case Report and Literature Review

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ABSTRACT

The clinical case of a 48-year-old patient with BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMA (BIA-ALCL) is presented. The clinical presentation, diagnosis methods, and treatment are described.

The case is combined with a bibliographic review that summarizes and analyses the history and epidemiology of this emerging pathology, of low incidence, but with a discrete malignant potential.

The growing use of breast implants around the world, both in breast reconstruction and aesthetics, makes be aware of new publications that increase more robust evidence to the knowledge of this entity.

Keywords: BIA-ALCL (Breast Implant-Associated Anaplastic Large Cell Lymphoma), Clinical Presentation, Diagnosis, Therapy, Incidence

Introduction

We present the case of a 48-year-old female patient who consulted due to sudden onset of left breast enlargement and pain. She has a history of breast implant surgery 8 years ago, smoked 2 cigarettes/day since the age of 17, with no family or personal history of cancer. Obstetric history G3P3A0. Physical examination reveals medium-sized breasts, bilateral old surgical scars, slightly enlarged asymmetric left breast with ascended left implant. There were no palpable nodules in breasts nor in ganglion territories. The rest of the physical exam is normal.
Imaging Study

A Mammogram was requested (Fig. 1), showing extremely dense breasts tissue without nodules or suspicious microcalcifications. The left implant was smaller in size and with a folded surface. An area of greater density was observed around the implant. Breast ultrasound (Fig. 2) reported a moderate amount of fluid (seroma) in the periphery of the left implant with echogenic septa, maximum thickness of 23 mm. The study was completed with breast magnetic resonance imaging (Fig. 3), which reported "peri-prosthetic fluid and impregnation of the external capsule of the left implant, findings that could be in the context of an inflammatory condition."

With these findings, aspiration and study of the peri-prosthetic fluid under ultrasound vision was requested.

![Figure 1: Bilateral midlateral oblique (a) and craniocaudal (b) mammographic projections](image1)

The left breast image shows size-reduced implant with some folds, suggestive of capsular contracture. A dense periprosthetic band (white arrow) is observed in the peripheric area of the implant, corresponding to liquid that surrounds it.

![Figure 2: Complementary ultrasound](image2)
Image (c) shows that the left periprosthetic fluid has multiple non-vascularized septa (long arrow). Image (d) shows a preserved ipsilateral axillary lymph node (short arrow).

![Figure 3: Breast MRI](image)

In contrast-enhanced MRI, hyperintense periprosthetic fluid with septa can be seen. In the T1 contrast sequence, a slight impregnation of the left capsule is observed, without an evident nodule. In the sagittal sequential image for silicone, the radiated folds of the implant are observed, without signs of rupture.

**Citologic, Histoquimicy Patologist Studies**

The cytological study reported a negative smear for malignant neoplastic cells with a background in proteinaceous parts including macrophages, some lymphocytes and polymorphonuclear cells.

Immunophenotyping was performed by flow cytometry (Fig. 4), which shows the T lymphoid population that corresponds to 76% of the total lymphoid population. 97% of the population presented immunophenotype characteristics of normal T cells, with adequate expression of CD3, CD5, CD4 (63%), CD8 (36%). A total of 2.7% of the T lymphoid population expressed positive gamma / delta receptor (blue), double negativity for CD4 and CD8, weak to moderate expression of CD3, CD5, weak for CD7, CD2, CD34 and weak CD1, negative for TdT which corresponds to 1.5% of global cellularity.
With these suspected elements of non-Hodgkin’s lymphoma immunophenotype T, the patient underwent implants removal surgery, including bilateral capsulectomy. Her post-operative was satisfactory. The removed implants were textured.

Microscopic examination of the surgical specimen (left peri-prosthetic capsule) showed isolated interstitial infiltration of the fibrocolagenous wall by large atypical cells with polylobulated hyperchromatic nuclei and a scant to moderate amount of pale eosinophilic cytoplasm, some cells had a Hodgkinoid appearance (Fig. 5 and Fig. 6). Immunohistochemical studies of the tissue showed that these cells were positive for CD30 (Fig. 7) with co-expression of CD43, and negative for CD3 and ALK-1.

The result of the definitive biopsy was BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL IMMUNOPHENOTYPE T NON-HODGKIN LYMPHOMA.

Figure 4: Immunophenotype study of peri-prosthetic fluid

Figure 5: (with 200X and 400X Hematoxylin & Eosin staining) show lymphoid infiltration of the prosthetic capsule, especially of small, mature cells. Neoplastic cells are larger, with prominent vesicular nuclei and nucleoli
Figure 6: The prosthetic capsule, Positive immunoreaction for CD30 in neoplastic cells

Figure 7: Capsule removed in surgery

The patient is presented to the oncology committee. Strict clinical monitoring is recommended, as there is no indication for other types of adjuvant treatments such as chemotherapy or radiotherapy. A PET/CT Scan is requested, but the patient rejects it. Two years after the diagnosis of BIA-ALCL, the patient is in good general condition with no evidence of disease.

**Clinical Case Combined with Literature Review (Squires)**

Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) is a type of Non-Hodgkin Lymphoma, extranodal T lineage, recognized in the WHO classification since 2016.

Primary breast lymphoma corresponds to 1–2% of all non-Hodgkin's lymphomas, the most common are: diffuse large B-cell lymphoma, follicular lymphoma, and marginal zone cell lymphoma. Only 10% of this group corresponds to implant-associated T immunophenotype ALCL (Laurent *et al.*, 1997).
The first case of BIA-ALCL was described in 1997 in a 41-year-old patient who presented a mass included in the capsule of one of her esthetics saline implants (Keech and Creech, 1997). Since then, the FDA (Food and Drug Administration) has reported 573 cases and 33 deaths worldwide (FDA (Safety communication on BIA – ALCL), 2019)

Most of the cases has only local involvement and can be effectively cured by surgical removal of the capsule (capsulectomy) and the implant. A small percentage of patients may have widespread dissemination, requiring systemic therapies.

The characterization of this new disease has been difficult, requiring 20 years of information gathering that has gained relevance given the massive use of breast implants in the world, either for aesthetics reasons or for breast reconstruction after a mastectomy. In 2010, Brody presented 34 cases of women diagnosed with ALCL in breast with an implant (Brody et al., 2010). This prompted the FDA to conduct a review of the literature on potential published cases. They found that, from January 1997 to May 2010, there were 34 unique cases of ALCL in women with breast implants published worldwide (Center for Devices and Radiological Health Food and Drug Administration (FDA), 2011). However, the number rose to 60 cases when accounting submitted by scientific experts, implant manufacturers or regulatory authorities were included. Given the possible duplication of data in the scientific literature available at that time it was difficult to accurately estimate the number of cases. With this limited information, it was not possible to confirm with statistical certainty that breast implants caused ALCL. It was concluded that women could have a very small risk of developing this disease in the implant capsule, and it was not possible to determine risk factors (Center for Devices and Radiological Health Food and Drug Administration (FDA), 2011). In 2011, the FDA reported for the first time a possible relationship between silicone or saline breast implants and the development of ALCL, highlighting that the incidence was very low. Nevertheless, it recommended the collection of information on this matter (Center for Devices and Radiological Health Food and Drug Administration (FDA), 2011).

In 2015, Brody published a larger series of 173 cases, reviving world’s interest in this emerging entity (Torres Pérez et al., 2020; Brody et al., 2015). In 2016, the WHO (World Health Organization) recognized this disease as a rare type of cancer and designated it as BIA - ALCL (Breast implant-associated anaplastic large cell lymphoma), recognizing this particular type of T-cell lymphoma as an entity on its own (Swerdlow et al., 2016) After this the reports increased globally, although the data remain imprecise due to lack and/or failure of records of implants users (aesthetics, breast reconstruction) or due to unknown type of implants, lack of clinical history, or data duplication, among others.
In 2017, Australia and New Zealand reported together 55 cases with 4 deaths in a series of patients between 2007 and 2016 (Loch-Wilkinson et al., 2017). In the same year at the request of the European Commission, the Scientific Committee on Environmental Health and Emerging Risks (SCHEER) published a similar document, as the US agency, stating that although there were new cases of ALCL in women with implants worldwide suggesting an association, there was not (at that time) enough scientific information available to conduct a robust risk assessment for which further prospective studies were needed. Thus, still it was not possible to provide evidence-based conclusions (SCHEER, 2017).

Later, in the United States in 2018, the American Society of Plastic Surgeons published a prospective registry created in 2012 (PROFILE), which collected information on new 257 cases of BIA–ALCL (McCarthy et al., 2019). That same year the FDA issued a new safety notice (FDA, 2018) based on 414 reports of adverse events on BIA–ALCL, including the death of 9 patients. On that occasion, data of implants ‘surface type was provided in 272 cases. From them, 242 (88.9%) had textured implants and 30 smooth implants surface. However, they highlighted that, in the cases diagnosed with smooth implants, the patients had a previous history of implant use or there was not enough information to review this with certainty (FDA, 2018). It was also reported that the filling of the implant did not seem to influence the incidence of this pathology. Half of the reported cases were diagnosed within 7 to 8 years of implant placement. With the available information the FDA concluded that most of the data suggested that BIA–ALCL would occur more frequently when textured surface implants were used. Moreover, it was estimated that BIA–ALCL could develop in 1 in 3,817 to 30,000 women with textured implants. (Clemens et al., 2019).

In February 2019, the FDA updated the number of adverse effects, reporting 660 cases of BIA–ALCL (FDA (Advisory Committee Meeting), 2019); a more exhaustive analysis suggested that there were 457 unique cases. In mid-March 2019, the FDA issued warning letters to two breast implant manufacturers: Mentor Worldwide LLC. Irvine, California, (FDA (WARNING LETTER Mentor Worldwide LLC & Acclarent MARCS-CMS), 2019) and Sientra, Inc. Santa Bárbara, California (FDA (WARNING LETTER Sientra Inc MARCS-CMS), 2019). This, for not complying with studies of risks and long-term safety of their silicone gel breast implants. All approved silicone gel breast implant manufacturers had to (and should) conduct post-FDA approval studies to further evaluate the safety and efficacy of their products, in order to provide additional data of potential risks and long-term safety of their breast implants (FDA (Advisory Committee Meeting), 2019).

As more information is collected, interest and concern grows around the world to better understand this new pathological entity. Thus, at the end of March 2019, a Panel of Experts was
convened in Silver Spring, Maryland, headquarters of the FDA, where the issue was discussed. They concluded not to restrict textured implants. This has also been recommended by other institutions such as the International Society of Aesthetic Plastic Surgery (ISAPS) (FDA (WARNING LETTER Sientra Inc MARCS-CMS), 2019). Despite this, some countries such as France, Canada and Australia decide to put restrictions and/or withdraw textured implants from their markets, although they do not recommend their preventive withdrawal in patients who have them.

In July 2019, the FDA provides new information declaring 573 cases of BIA–ALCL worldwide, with 33 patient deaths (FDA News Release, 2019). Of the 573 cases, 481 (83.9%) were related to ALLERGAN TM implants (manufacturer of a type of textured implants). In 12 of the 13 death cases, patients had an ALLERGAN brand implant, only one was unknown. New data and information are added and analyzed since the March meeting in Maryland, concluding that the risk of presenting BIA–ALCL with ALLERGAN BIOCELL Textured Implants was approximately 6 times higher than with textured implants from other manufacturers. As a result, the FDA requested ALLERGAN to withdraw from the US market specific models of its implants due to the risk of presenting BIA–ALCL. Thereafter ALLERGAN notified the voluntary worldwide withdrawal from the market of its BIOCELL textured implants and expanders. The FDA made a clear statement that did not recommend the prophylactic removal of implants in asymptomatic patients (FDA News Release, 2019).

This historical review summarizes the long and difficult path to characterize this disease for which is still necessary to identify risk factors, know its pathogenesis and determine its incidence more accurately. Therefore, it is not yet possible to determine the risk of developing a BIA-ALCL.

There is no consensus on the true frequency of this disease, which is to be expected, given that at least 10 million women worldwide have breast implants (550,000 new implants per year in the United States) making difficult the data collection (Mehta-Shah et al., 2019). BIA–ALCL has been classified as an extremely infrequent and rare disease compared at first with the possibility of "being hit by an asteroid" (Clemens, 2019).

As more knowledge of the disease is gathered, information of risk estimation and incidence increases. Initially, the risk of developing BIA–ALCL was estimated to be 1 to 3 per million women with implants per year (Zerga, 2018; Doren et al., 2017). In the United States, estimation was of 1 case in 300,000 women with breast implants per year; however, with textured implants, incidence is higher, being 33 per million people with a lifetime prevalence of 1 in 3,000 (Marra et al., 2020).

Australian series show that the risk of developing BIA-ALCL ranges from 1: 2,832 to 1: 86,029 in textured implants, with textures grade 3 and 4 appearing to have higher risk than grades 2 and 1 (the
higher the degree of texture, the greater the risk) (Groth and Graf, 2020). Australia reports a higher incidence of this disease than other countries, this could be explained to some extent because textured implants are used more in that country, while countries such as the United States and Canada tend to use smooth implants (Zerga, 2018; Groth and Graf, 2020; Magnusson et al., 2019).

More recently, Ghion published in 2019 that the risk varies between 1: 440 to 1: 86,000, depending on the implant type (Cordeiro et al., 2020). Most series estimate that the risk of textured BIA – ALCL ranges between 1/2832 and 1 / 30,000 women (Marra et al., 2020; Cordeiro et al., 2020). As previously mentioned, the FDA estimates that BIA – ALCL could developed in 1 in 3,817 to 30,000 women with textured implants. When analyzed by age, the incidence rate is 1 / 35,000 in patients 50 years old, 1 / 12,000 at 70 years and 1 / 7,000 at 75 years old (de Boer M et al., 2018) Finally, Clemens, one of the authors who has published the most on BIA – ALCL agrees that risk varies between 1: 440 to 1: 86,000 depending on the specific risk of the implant (Clemens, 2019; Cordeiro et al., 2020).

In summary, the information currently available shows that BIA – ALCL is a rare and infrequent disease associated with the use of textured breast implants used for cosmetic purposes or for breast reconstruction.

Etiology and Pathogenesis

The etiology and pathogenesis of BIA – ALCL have not yet been clearly elucidated. The most frequently mentioned theories in the literature refer to a possible role of chronic inflammation caused by textured implants (Marra et al., 2020; Laurent et al., 2020). This could trigger an immune response in some patients in the context of a possible allergic reaction. It is also mentioned that the bacterial biofilm plus the patient’s own microbiota could influence the pathogenesis (Marra et al., 2020; Laurent et al., 2020).

In relation to genetic predisposition of BIA – ALCL, there are studies that have identified mutations associated with a higher risk of BIA – ALCL. Activating mutations and loss-of-function alterations of epigenetic modifiers have been described; Laurent characterized the genomic panorama of 34 BIA – ALCL (15 tumor subtypes and 19 in situ) collected from 54 patients (Marra et al., 2020; Laurent et al., 2020)

Clinical Presentation

The most common presentation of BIA – ALCL, described in patients with textured surface implants, is a sudden increase in breast volume at the expense of the development of a seroma.
Although there are some published cases of patients with smooth implants, the patients had had previously textured implants, or this data was not described (Clemens et al., 2018; Brody et al., 2015).

This seroma has a late presentation, at least 1 year after surgery, with an average presentation of 7 to 10 years after the implants, either for cosmetic reasons or breast reconstruction (Clemens et al., 2019; Brody et al., 2015). Different studies confirm this form of presentation (seroma formation), in 70 to 80% of cases. About 20% of the seromas appear as a breast mass adjacent to the implant’s capsule (Clemens, 2020; Clemens et al., 2016) Other less frequent presentations are: the presence of regional nodes, capsular contracture, skin rash, breast pain, or fever, altogether reaching 5% of cases. Our patient had an abrupt development of a seroma, pain, breast enlargement and asymmetry, 8 years after surgery.

**Study and Diagnosis**

The imaging study includes a mammogram that usually does not provide enough information in this pathology since it is less sensitive to effusions and / or masses without calcifications (Clemens et al., 2019). However, it can be useful to detect the presence of a dense peri-implant band, with a sensitivity of 70%.

Breast ultrasound is the examination that best characterizes this disease since it confirms the presence of a seroma and / or peri-prosthetic mass and / or lymph nodes. Ultrasound has better sensitivity (84%) in detecting peri-implant fluid (Brody et al., 2015). In our case, the patient’s ultrasound confirmed the presence of a large left peri-implant seroma.

Magnetic resonance imaging can aid in the diagnosis of soft tissue masses. It is used to complete information or in those cases in which the ultrasound is equivocal (Adrada et al., 2014).

Normally, around the implants there is a small amount of fluid, between 5 and 10 cc (Clemens et al., 2019). Greater amount of fluid, which confirms a seroma, is expected until the first year after surgery. However, only 1% of patients have a later seroma. Eisenberg et al. suggest that any seroma that appears after one year after surgery should be studied with culture, cytology, flow cytometry and cell block (Eisenberg et al., 2018).

Fine needle aspiration of the seroma is the next recommended study step, with a minimum of 50 cc collection. The liquid tends to be cloudy, with “debris” and can sometimes vary from amber to creamy white or yellowish liquid, simulating an infection.

If the presence of a mass is detected, a core biopsy under ultrasound vision is recommended. The
immunophenotype study evidences positive expression of CD30, with incomplete expression of some of the pan T antigens (CD2, CD3, CD5, CD7) and they are also generally CD4 positive.

**Treatment**

The recently updated guidelines of the National Comprehensive Cancer Network (NCCN) in 2019, states that the treatment of choice for patients with BIA – ALCL is surgical excision of the implant, the capsule, and any associated mass (Clemens et al., 2019).

Timely diagnosis, as well as multidisciplinary management are essential for this disease, which, although cataloged as low risk, has malignant potential that can cause death in a small subgroup of patients. Complete surgical excision has been shown to increase overall survival (p = 0.001) and event-free survival (p = 0.001) compared to all other therapeutic interventions (Torres Pérez et al., 2020; Clemens et al., 2019).

The value of sentinel node biopsy or radical mastectomy remains unclear. Axillary emptying has been used in few cases of armpit positive nodes. In a literature review it was found that, out of a group of 22 cases with documented advanced disease, only 4 cases underwent axillary emptying (Clemens et al., 2019). Overall 5-year survival is significantly less in patients with lymphatic involvement at the time of diagnosis. (75% vs 97.9% in patients with and without lymph node involvement, respectively) (Marra et al., 2020).

Overall, most of the cases have only local involvement and can be effectively cured with implant removal and capsulectomy, a small percentage experience relapses and dissemination, requiring systemic therapies. Additionally, the NCCN has promoted a specific TNM staging for BIA – ALCL (Clemens et al., 2019). Most patients have early stage disease (83% stage IE; 10-16% stage IIE). Any BIA – ALCL with involvement of sites other than the ipsilateral breast and regional lymph nodes is considered stage IV disease. Patients with stage I disease can be treated with surgery only, as was the case with our patient.

**Conclusions**

The literature review highlights that:

1. BIA – ALCL is an infrequent, low incidence disease, although with potential for malignancy.
2. It appears in patients using breast implants for aesthetics or breast reconstruction reasons.
3. It is more often associated with textured surface breast implants.
4. Its etiology is yet uncertain, with unclear risk factors.
5. Its most frequent form of presentation is the appearance of a sudden and delayed seroma in patients with textured breast implants.

6. Breast ultrasound is the most useful initial examination for its diagnosis.

7. Aspiration and study of the seroma liquid by flow cytometry and/or biopsy of a mass adhered to the capsule are the recommended procedures for diagnosis. Testing CD30IHC is required to confirm or rule out BIA-ALCL.

8. Treatment is mainly surgical: removal of implants plus capsulectomy and removal of mass, if any.

9. Its prognosis is favorable, achieving cure in most of the cases submitted to surgery.

10. Advanced cases may require adjuvant treatments such as chemotherapy, radiotherapy.

11. Multidisciplinary management is recommended (oncologic surgeon, hematologist, pathologist, radiologist).

12. As global awareness increases, with better data collection, it will be crucial to improve detection.

13. Prophylactic removal of textured implants is not recommended.

For more information, it is suggested to review the FDA report as of July 2019, available at: FDA safety communication on BIA-ALCL. https://www.fda.gov/medical-devices/breast-implants/medical-device-reports-breast-implant-associated-anaplastic-large-cell-lymphoma.

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