

BREAST IMPLANT ASSOCIATED- ANAPLASTIC LARGE CELL LYMPHOMA DEVELOPMENT CASE IN A SET OF DIZYGOTIC TWINS WITH BREAST IMPLANTS

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Summary

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is an uncommon malignancy occurring in women with breast implants. The risk for women carrying breast implants ranges from one in 300 to in 300.000 according to current epidemiological estimates. While many advancements have been made in the etiopathogenesis of the condition, little is known regarding its genetic background and its role in disease onset. Data regarding the possibility of genetic predisposition and/or familial inheritance are a matter of contention. We report a case of BIA-ALCL in a set of dizygotic twins, one of whom developed BIA-ALCL infiltrating beyond the capsule (pT4), while her sibling was negative for the disease after exposure to macrotextured breast implants for a similar duration. The aim of this report is to provide some additional, although anecdotal, evidence regarding the role of genetic predisposition in BIA-ALCL onset.

Key words: BIA-ALCL, breast implants, dizygotic twins, breast augmentation

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INTRODUCTION

Over the past decades, a distinct hematologic neoplasm has been described in patients with breast implants, and is known as breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) ¹. Its first report dates back to 1997, which was described by Keech and Creech ². This was followed much later by the Food and Drug Administration's initial report of 2011 ³. The World Health Organization acknowledged the existence of the condition in 2016 and categorized it as a separate nosological entity in the revised edition of the classification of lymphoid neoplasms ⁴. As recently stated by the Scientific Committee on Health, Environmental

and Emerging Risks, BIA-ALCL is correlated with the use of textured implants⁵. Epidemiological evidence has demonstrated this risk to be especially high with specific macrotextured devices (i.e. Allergan Biocell and Silimed Polyurethane), and lower with microtextured implants and macrotextured devices produced by other manufacturers⁶. The prevalence of BIA-ALCL in women with breast implants has been found to be of approximately 1 in 14:000 women in the European population⁷. Rarely does BIA-ALCL also occur bilaterally, with evidence suggesting that this occurrence affects around just 2% of affected patients⁸. Currently, no convincing evidence exists regarding the possibility of genetic predisposition and/or familial inheritance. This poses questions regarding the role of genetic factors in twins who both possess breast implants in which only one develops BIA-ALCL. We report our experience with dizygotic twin sisters who both received similar breast implants, though only one developed BIA-ALCL.

CASE PRESENTATIONS

A 52-year-old female underwent bilateral breast augmentation for cosmetic purposes in 1994, receiving McGhan 230 cc silicone macrotextured implants (formerly McGhan Medical Corporation, acquired by Allergan Inc., Dublin, Ireland) in the submuscular plane. Post-operative course was uneventful, with no abnormal findings in routine mammogram checks. In 2012, she noticed a nodule on the skin of the inferior-medial quadrant in her right breast. An excisional biopsy of the skin lesion was performed and the histopathology report described chronic granulomatous inflammation and dermal fibrosis. In 2013, the patient was referred to our institution and first came to our attention, complaining of right breast swelling with hardening and pain. A breast ultrasound revealed bilateral effusion, worse in the right side, which was managed conservatively. In 2015, due to the worsening of the symptoms, she repeated an ultrasound (US)/mammography and a Magnetic Resonance Imaging (MRI) scan, which confirmed the intracapsular effusion but also reported a 4-cm irregular area which was found in the internal equatorial quadrant of the periprosthetic capsule, which was defined as “adipositis or fat necrosis”. Soon thereafter, the patient underwent implant removal with total capsulectomy in 2016, and placement of Polytech 230 cc textured implants (POLYTECH Health & Aesthetics, Dieburg, Germany). Histology report of the right breast capsule revealed abundant fibrotic-necrotic tissue with marked lympho-histiocytic infiltrate, in which aggregates of large, atypical cells were found, bearing clear nuclei and high proliferative activity. Immunohistochemistry demonstrated that the atypical

cells were CD30, CD4, CD43, and Granzyme B positive, but ALK, CD3, CD8, CD20 negative, which is diagnostic for BIA-ALCL (Fig. 1). The cancer cells infiltrated soft tissues beyond the capsule, which was classified as a pT4 stage according to the MD Anderson-TNM classification⁹. The clinical stage of the neoplasia was settled after a CT-Scan. After diagnosis, the newly-placed implants were removed and a thorough surgical revision of the right periprosthetic pocket was performed. Repeat histology confirmed complete excision of the neoplasm. Immediate staging exams (CT-Scan and PET-CT) were negative for systemic metastases. Following a multidisciplinary discussion, adjuvant polychemotherapy was proposed for the locally infiltrating BIA-ALCL. However, the patient chose to seek a second opinion at another centre, where watchful waiting was chosen instead. Follow-up exams remained negative as of 2022, and the patient has been disease-free with no evidence of recurrence for 6 years after diagnosis (Fig. 2). The karyotype analysis on peripheral venous blood showed a normal diploid 46XX profile. In this case it was not possible to perform cytogenetic examination on capsule specimen. In fact, the lack of molecular and cytogenetic data on both patients and the fact that the twins were dizygotic, limited any hypothesis or conclusion on the possible role of the genetic predisposition in the pathogenesis of BIA-ALCL.

In 2017, the dizygotic twin sister of the patient also came to our attention. She had received a submuscular breast augmentation in 2006, when she was 52 years-old, with placement of Eurosilicone 375 cc macrotextured implants (Eurosilicone S.A.S., France). She complained of breast asymmetry with swelling of the right side which occurred progressively over the course of a year, with widespread

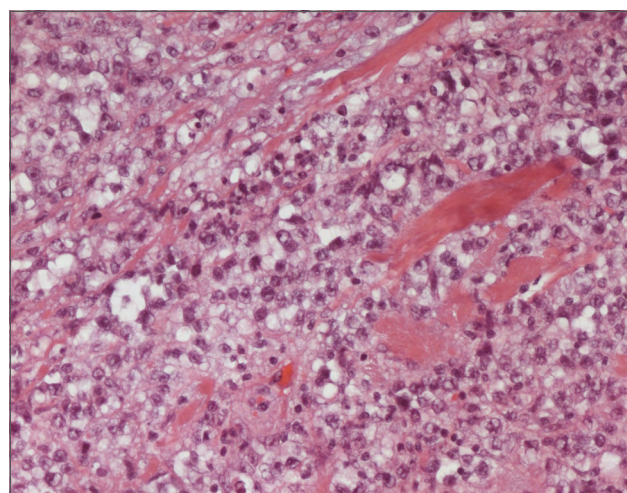


Figure 1. Hematoxylin and eosin-stained preparation of the patient affected by BIA-ALCL, showing thickened peri-implant capsule infiltrated by lymphoma cells.

hardening, pain and severe capsular contracture. US showed no periprosthetic effusion, nodularity or axillary lymphadenopathy. Consequently, she underwent total capsulectomy and implant replacement with Polytech 365 cc textured implants (Fig. 3). Histopathological examination of the capsules showed chronic histiocytic inflammation bilaterally, with no evidence of BIA-ALCL. A cytogenetic study was also carried out on 50 cells obtained from the culture of periprosthetic capsule fragments showing a mosaic karyotype 47, XXX(36)/46, XX(14), compared to the karyotype on peripheral venous blood which was a normal diploid 46, XX. Until this day, after 5 years of follow-up, the patient appears not to have developed BIA-ALCL.

DISCUSSION

Cytogenetic analysis of peripheral blood cells and periprosthetic capsules was performed on the patients with the aim of identifying any chromosomal abnormality associated with the disease, other than rearrangements which are characteristic of ALCL. The cytogenetic study of the blood samples in the affected patient, showed no chromosomal anomalies associated with the neoplasm but they weren't compared with the neoplasm cells cyto-analysis, not allowing us to make a specific cytogenetic diagnosis. It was also interesting to analyse the case of the patient's twin sister, who had macrotextured breast implants for about 10 years, showing only capsular contracture. When the implants were replaced, the search for BIA-ALCL was negative. A relevant consideration is that the twin sister had received Eurosilicone devices, which have been associated with a lower incidence risk of BIA-ALCL compared to Allergan and other macrotextured implants ⁶.

A cytogenetic examination was performed on the twin sister as well to identify any predictive chromosomal abnormality. Some of the distinct cytogenetic features shown in ALCL include a reciprocal translocation t(2;5) involving the chromosomes 2p23 and 5q35, which results in the fusion of the ALK gene with the *NPM1* gene. This fusion produces a chimeric protein (p80) with autonomous phosphorylating activity ¹⁰. However, BIA-ALCL does not have the same chromosomal rearrangements typical to other types of ALCL ¹¹. Although only on an anecdotal level, this notion was corroborated by our findings. Some of the most detected genetic alterations include mutations in JAK/STAT signalling pathway genes, TP53 and DNMT3A ¹².

In our study, BIA-ALCL diagnosis became apparent almost 20 years after the breast implantation, which is considerably longer than the reported median time of onset which is of approximately 10 years ¹³. Considering



Figure 2. Patient with periprosthetic right bright effusion in a history of bilateral breast augmentation with McGhan 230 cc silicone macrotextured implants (on the left), who received total capsulectomy and breast implant replacement with Polytech 230 cc textured implants (on the right), before BIA-ALCL diagnosis. Asterisk shows where skin biopsy was performed.



Figure 3. BIA-ALCL patient's twin sister who received bilateral breast augmentation with Eurosilicone 375 cc macrotextured implants (on the left), who received total capsulectomy and breast implant replacement with Polytech 265 cc textured implants (on the right), with no BIA-ALCL diagnosis.

the absence of local or distant metastases at the PET-Scan examination, the neoplasm was classified as stage IIA. We acknowledge that at the time, the case was neither diagnosed nor treated according to best practice standards outlined in the National Comprehensive Cancer Network (NCCN) recommendations of 2017 ¹⁴, and 2019 ¹⁵. This is due to the fact that the case came to our attention before the condition was fully acknowledged at our institution. While it is true that Italy described a diagnostic and treatment work-up as early as 2015, it was updated and gained popularity in 2019, leading to its nation-wide implementation ¹⁶. Aspiration cytology of the periprosthetic effusion was not performed when noticed in US/MRI exams: not sampling the periprosthetic effusion for cytological characterization likely lead to a diagnostic delay, which might have caused a progression of the disease with local invasion outside of the periprosthetic capsule. Additionally, the affected patient

did not receive an en-bloc capsulectomy for the treatment of the condition¹⁷. Thankfully, the patient did not require any adjuvant treatment as she appears to be free from recurrences at 6 years of follow-up. It is worth noting that when surgery cannot be radical, the role of adjuvant options has not been clearly defined¹⁸. This is particularly relevant, since radical en-bloc capsulectomy is the only treatment option which has demonstrated an improvement of patient survival¹⁷, unlike any other adjuvant treatment currently used for managing BIA-ALCL cases. Following the NCCN and Italian Guidelines, if the peri-prosthetic capsule has been totally removed with negative surgical margins and the surgical revision was histologically negative, the surgery could be considered totally radical. Moreover, if the CT/PET scan doesn't show any lymphnodes or tissues areas of pathological FDG up-take, radiotherapy and immuno-chemotherapy are not recommended. Despite some anecdotal successes, the role of adjuvant radiotherapy, chemotherapy and immunotherapy (Brentuximab vedotin) and their efficacy in treating locally advanced and systemic cases is still uncertain since no clinical trial exists to support their use^{8,14}. In fact, NCCN recommendations for these treatment options are only based on guidelines for similar ALCLs, for lack of better evidence. This case serves as a cautionary tale to warn about the risks of delayed BIA-ALCL diagnosis, which poses the risk of non-radical surgery with potential spread of disease, as well as the higher morbidity caused by subsequent reoperations for complete cancer excision. Many elements of BIA-ALCL remain elusive. This includes its etiopathogenesis as well as its most appropriate management of advanced cases. Managing suspicious or confirmed cases has been discussed extensively in literature¹⁹. However, a challenge we faced when managing this case consisted in the lack of evidence to support the management of the unaffected twin sister and her breast implants. We hope that literature and future evidence will help elucidating the role of the preventive management of patients with macrot textured breast implants. The disclosure of the risk of BIA-ALCL should have as its main objective to make patients aware of the existence of this uncommon disease and, by understanding the onset symptoms, induce patients to consult a specialist for an early diagnosis²⁰⁻²³.

CONCLUSIONS

The aim of future research will be to determine whether and environmental risk factors are able to influence the onset of the disease, particularly in relation to the surgical technique and the type of implant. At present, it is

not yet possible to provide definitive conclusions on the BIA-ALCL risk factors in relation to the patient, because of the absence of extensive epidemiological studies that can clarify the subject matter. On the whole, limitations in our cases and in their follow-up were present: the lack of molecular and cytogenetic data on both patients and the dizygotic twins-status, limited any hypothesis or conclusion on the possible role of the genetic predisposition in the pathogenesis of BIA-ALCL. Moreover, the shorter time to surgery of the second sister (11 years vs 22 years) could not exclude that she would develop BIA-ALCL as well, limiting speculations on the possible role of environmental risk factors. That's why we aim to suggest, with our experience, further investigations and research about the possible genetic predisposition in BIA-ALCL development.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

CL, AL: A.
MC, PA: D.
FM, NI: DT.
FL, DP: S.
MC: W.

Abbreviations

A: conceived and designed the analysis
D: collected the data
DT: contributed data or analysis tool
S: performed the analysis
W: wrote the paper
O: other contribution (specify contribution in more detail)

ETHICAL CONSIDERATION

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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